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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under **37 CFR 1.53** (c).

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TITLE OF THE INVENTION (500 characters max)

HIV INTEGRASE INHIBITORS

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

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EXPRESS MAIL CERTIFICATE

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In Duplicate

TITLE OF THE INVENTION
HIV INTEGRASE INHIBITORS

The present invention is directed hydroxy tetrahydro-2,6-naphthyridine dione and hydroxy hexahydro-2,6-naphthyridine dione compounds and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds and pharmaceutically acceptable salts thereof of the present invention are useful for preventing or treating infection by HIV and for preventing or treating or delaying the onset of AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of +proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhbitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase in vitro and HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected cells. The particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

The following references are of interest as background:

US 6380249, US 6306891, and US 6262055 disclose 2,4-dioxobutyric acids and acid esters useful as HIV integrase inhibitors.

WO 01/00578 discloses 1-(aromatic- or heteroaromatic-substituted)-3-(heteroaromatic substituted)-1,3-propanediones useful as HIV integrase inhibitors.

US 2003/0055071 (corresponding to WO 02/30930), WO 02/30426, and WO 02/55079 each disclose certain 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors.

WO 02/036734 discloses certain aza- and polyaza-naphthalenyl ketones to be HIV integrase inhibitors.

WO 03/016275 discloses certain compounds having integrase inhibitory activity.

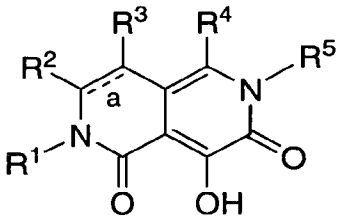
WO 03/35076 discloses certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors, and WO 03/35077 discloses certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

WO 03/062204 discloses certain hydroxynaphthyridinone carboxamides that are useful as HIV integrase inhibitors.

WO 04/004657 discloses certain hydroxypyrrole derivatives that are HIV integrase inhibitors.

SUMMARY OF THE INVENTION

The present invention is directed to hydroxy polyhydro-2,6-naphthyridine dione compounds. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS and/or ARC, either as compounds or their pharmaceutically acceptable salts or hydrates (when appropriate), or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention includes compounds of Formula I, and pharmaceutically acceptable salts thereof:



(I)

wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

R^1 is -C_{1-6} alkyl substituted with R^J, wherein R^J is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently:

(1) -C_{1-6} alkyl optionally substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)R^b$, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$OC(=O)N(R^a)R^b$, or -$N(R^a)C(=O)N(R^a)R^b$,

(2) -O-C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} haloalkyl,

(5) -OH,

(6) halogen,

(7) -CN,

(8) -NO_2,

(9) -$N(R^a)R^b$,

(10) -$C(=O)N(R^a)R^b$,

(11) -$C(=O)R^a$,

(12) -CO_2R^a,

(13) -SR^a,

(14) -$S(=O)R^a$,

(15) -SO_2R^a,

(16) -$SO_2N(R^a)R^b$,

(17) -$N(R^a)SO_2R^b$,

(18) -$N(R^a)SO_2N(R^a)R^b$,

(19) -$N(R^a)C(=O)R^b$,

(20) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$, or

(21) -$N(R^a)CO_2R^b$, and

(b) optionally substituted with 1 or 2 substituents each of which is independently:

(1) phenyl,

(2) benzyl,

(3) -HetA,

(4) -C(=O)-HetA, or

(5) -HetB;

wherein each HetA is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with from 1 to 4 substituents each of which is independently oxo or C_{1-6} alkyl; and

wherein each HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; and

(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C_{1-6} alkyl substituted with aryl;

R^2 and R^3 are each independently -H or -C_{1-6} alkyl;

R^4 is:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -C_{1-6} alkyl substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO_2R^a, -C(=O)-N(R^a)-C_{1-6} alkylene-OR^b with the proviso that the -N(R^a)- moiety and the -OR^b moiety are not both attached to the same carbon of the -C_{1-6} alkylene- moiety, -$S(O)_nR^a$, -SO_2N(R^a)R^b, -N(R^a)C(=O)-R^b, -N(R^a)CO_2R^b, -N(R^a)SO_2R^b, -N(R^a)SO_2N(R^a)R^b, -N(R^a)C(=O)N(R^a)R^b, or -OC(=O)N(R^a)R^b,

(5) $-C(=O)R^a$,

(6) $-CO_2R^a$,

(7) $-C(=O)N(R^a)R^b$,

(8) $-C(=O)-N(R^a)-C_{1-6}$ alkylene-OR^b with the proviso that the $-N(R^a)-$ moiety and the $-OR^b$ moiety are not both attached to the same carbon of the $-C_{1-6}$ alkylene- moiety,

(9) $-N(R^a)-C(=O)-R^b$,

(10) $-N(R^a)-C(=O)-C(=O)N(R^a)R^b$,

(11) $-N(R^a)SO_2R^b$,

(12) $-N(R^a)SO_2N(R^a)R^b$,

(13) $-N(R^a)SO_2N(R^a)R^b$,

(14) $-N(R^a)C(=O)N(R^a)R^b$,

(15) $-OC(=O)N(R^a)R^b$,

(16) $-R^K$,

(17) $-C(=O)-R^K$,

(18) $-C(=O)N(R^a)-R^K$,

(19) $-C(=O)N(R^a)-C_{1-6}$ alkylene-R^K,

(20) $-C_{1-6}$ alkyl substituted with $-R^K$,

(21) $-C_{1-6}$ alkyl substituted with $-C(=O)-R^K$,

(22) $-C_{1-6}$ alkyl substituted with $-C(=O)N(R^a)-R^K$, or

(23) $-C_{1-6}$ alkyl substituted with $-C(=O)N(R^a)-C_{1-6}$ alkylene-R^K;

wherein R^K is

(i) C_{3-8} cycloalkyl, which is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, or $-O-C_{1-6}$ haloalkyl,

(ii) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently $-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene-OH, $-C_{1-6}$ alkylene-$O-C_{1-6}$ alkyl, $-C_{1-6}$ alkylene-$O-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkylene-$N(R^a)R^b$, $-C_{1-6}$ alkylene-$C(=O)N(R^a)R^b$, $-C_{1-6}$ alkylene-$C(=O)R^a$, $-C_{1-6}$ alkylene-CO_2R^a, $-C_{1-6}$ alkylene-$S(O)_nR^a$, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ haloalkyl, -OH, halogen, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, or $-SO_2N(R^a)R^b$;

(iii) HetK, which is a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:

(a) optionally substituted with from 1 to 6 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(b) optionally substituted with aryl or HetC;

wherein HetC is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and the optionally fused heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; or

(iv) HetL, which is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

R^5 is:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -C_{3-8} cycloalkyl optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(4) -C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(5) -C_{1-6} alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-$N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)R^a$, -C_{1-6} alkylene-CO_2R^a, -C_{1-6} alkylene-$S(O)_nR^a$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halogen, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, or $-SO_2N(R^a)R^b$;

(6) -C_{1-6} alkyl substituted with HetD, wherein HetD is

(i) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is optionally substituted with from 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; or

(ii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

each aryl is independently phenyl, naphthyl, or indenyl;

each R^a is independently H or C_{1-6} alkyl;

each R^b is independently H or C_{1-6} alkyl; and

each n is independently an integer equal to zero, 1, or 2.

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of Formula I above, and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts are HIV integrase inhibitors.

A first embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; and all other variables are as originally defined (i.e., as defined in the Summary of the Invention).

A second embodiment of the present invention is a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; R^J is phenyl, quinolinyl, isoquinolinyl, cinnolinyl, or quinazolinyl, any of which is:

(a) optionally substituted with from 1 to 4 substituents each of which is independently:
  (1) -C_{1-4} alkyl,
  (2) -O-C_{1-4} alkyl,
  (3) -C_{1-4} haloalkyl,
  (4) -O-C_{1-4} haloalkyl,
  (5) halogen,
  (6) -CN,
  (7) -$N(R^a)R^b$,
  (8) -$C(=O)N(R^a)R^b$,
  (9) -$S(=O)R^a$,
  (10) -SO_2R^a,
  (11) -$N(R^a)SO_2R^b$,
  (12) -$N(R^a)SO_2N(R^a)R^b$,
  (13) -$N(R^a)C(=O)R^b$, or
  (14) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$, and

(b) optionally substituted with 1 or 2 substituents each of which is independently:
  (1) -HetA, or
  (2) -C(=O)-HetA;

wherein each HetA is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-4} alkyl; and with the proviso that when HetA is attached to the rest of the compound via the -C(=O)- moiety, the HetA is attached to the -C(=O)- via a ring N atom;

and all other variables are as originally defined.

A third embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; R^J is phenyl optionally substituted with from 1 to 3 substitutents each of which is independently:

  (1) -C_{1-4} alkyl,
  (2) -C_{1-4} haloalkyl,
  (3) -O-C_{1-4} alkyl,
  (4) halogen,

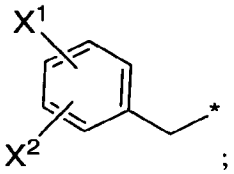
(5) -CN, or

(6) $-C(=O)N(R^a)R^b$, or

(7) $-SO_2R^a$;

and all other variables are as originally defined.

A fourth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



;

the asterisk * denotes the point of attachment of R^1 to the rest of the compound; X^1 and X^2 are each independently:

(1) -H,

(2) $-C_{1-6}$ alkyl,

(3) $-O-C_{1-6}$ alkyl,

(4) $-C_{1-6}$ haloalkyl,

(5) $-O-C_{1-6}$ haloalkyl,

(6) halogen,

(7) -CN,

(8) $-N(R^a)R^b$,

(9) $-C(=O)N(R^a)R^b$,

(10) $-S(O)_nR^a$, wherein n is an integer equal to zero, 1, or 2,

(11) $-N(R^a)SO_2R^b$,

(12) $-N(R^a)SO_2N(R^a)R^b$,

(13) $-N(R^a)C(=O)R^b$,

(14) $-N(R^a)C(=O)-C(=O)N(R^a)R^b$,

(15) -HetA,

(16) -C(=O)-HetA, or

(17) HetB;

wherein each HetA is independently a C_{4-5} azacycloalkyl or a C_{3-4} diazacycloalkyl, either of which is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-6} alkyl; and with the proviso that when HetA is

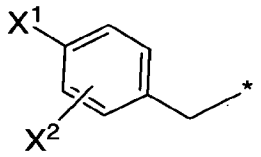
attached to the rest of the compound via the -C(=O)- moiety, the HetA is attached to the -C(=O)- via a ring N atom; and

each HetB is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

and all other variables are as originally defined.

An aspect of the fourth embodiment is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein X^1 and X^2 are each independently: (1) -H, (2) -C_{1-4} alkyl, (3) -C_{1-4} haloalkyl, (4) -O-C_{1-4} alkyl, (5) halogen, (6) -CN, (7) -C(=O)NH_2, (8) -C(=O)NH(-C_{1-4} alkyl), (9) -C(=O)N(-C_{1-4} alkyl)$_2$, or (10) -SO_2-C_{1-4} alkyl; and all other variables are as defined in the fourth embodiment.

A fifth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



the asterisk * denotes the point of attachment of R^1 to the rest of the compound; X^1 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, or (5) methoxy; X^2 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, (5) methoxy, (6) -C_{1-4} alkyl, (7) -CF_3, (8) -O-C_{1-4} alkyl, (9) -OCF_3, (10) -CN, or (11) -SO_2(C_{1-4} alkyl); and all other variables are as originally defined.

A sixth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2-R^J; R^J is 4-fluorophenyl; and all other variables are as originally defined.

A seventh embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -C_{1-6} alkyl substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)$-R^b, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$N(R^a)C(=O)N(R^a)R^b$, or -$OC(=O)N(R^a)R^b$,

(5) -$C(=O)R^a$,

(6) -CO_2R^a,

(7) -$C(=O)N(R^a)R^b$,

(8) -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b,

(9) -$N(R^a)$-$C(=O)$-R^b,

(10) -$N(R^a)$-$C(=O)$-$C(=O)N(R^a)R^b$,

(11) -$N(R^a)SO_2R^b$,

(12) -$N(R^a)SO_2N(R^a)R^b$,

(13) -R^K,

(14) -$C(=O)$-R^K,

(15) -$C(=O)N(R^a)$-R^K,

(16) -$C(=O)N(R^a)$-C_{1-6} alkylene-R^K,

(17) -$(CH_2)_{1-3}$-R^K,

(18) -$(CH_2)_{1-3}$-$C(=O)$-R^K,

(19) -$(CH_2)_{1-3}$-$C(=O)N(R^a)$-R^K, or

(20) -$(CH_2)_{1-3}$-$C(=O)N(R^a)$-C_{1-6} alkylene-R^K;

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An eighth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) -H, (2) -C_{1-6} alkyl, (3) -C_{1-6} fluoroalkyl, (4) -CO_2R^a, (5) -$C(=O)N(R^a)R^b$, (6) -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b, (7) -$N(R^a)$-$C(=O)$-R^b, (8) -$N(R^a)SO_2R^b$, (9) -$N(R^a)SO_2N(R^a)R^b$, (10) -R^K, (11) -$C(=O)$-R^K, or (12) -$C(=O)N(R^a)$-$(CH_2)_{0-2}$-R^K; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An aspect of either the seventh embodiment or the eighth embodiment is a compound of Formula I, or a pharmaceutically acceptable thereof, wherein R^K is:

(i) C_{3-6} cycloalkyl, which is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(ii) phenyl, which is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-$N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)N(R^a)R^b$,

$-C_{1-6}$ alkylene-$C(=O)R^a$, $-C_{1-6}$ alkylene-CO_2R^a, $-C_{1-6}$ alkylene-$S(O)_nR^a$, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ haloalkyl, -OH, halogen, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, or $-SO_2N(R^a)R^b$;

(iii) HetK, which is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or oxo; or

(iv) HetL, which is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, or $-O-C_{1-6}$ haloalkyl;

and all other variables are as defined in the seventh or the eighth embodiment.

A ninth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) -H, (2) $-C_{1-4}$ alkyl, (3) $-CO_2H$, (4) $-C(=O)-O-C_{1-4}$ alkyl, (5) $-C(=O)NH_2$, (6) $-C(=O)NH-C_{1-4}$ alkyl, (7) $-C(=O)N(C_{1-4}$ alkyl$)_2$, (8) $-C(=O)-NH-(CH_2)_{2-3}-O-C_{1-4}$ alkyl, (9) $-C(=O)-N(C_{1-4}$ alkyl$)-(CH_2)_{2-3}-O-C_{1-4}$ alkyl, (10) -HetK, (11) -C(=O)-HetK, (12) $-C(=O)NH-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl), (13) $-C(=O)N(C_{1-4}$ alkyl$)-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl) (14) $-C(=O)NH-CH_2$-phenyl, or (15) $-C(=O)N(C_{1-4}$ alkyl$)-CH_2$-phenyl; wherein:

HetK is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 3 substituents each of which is independently $-C_{1-4}$ alkyl or oxo; and with the proviso that when HetK is attached to the rest of the compound via the -C(=O)- moiety, the HetK is attached to the -C(=O)- via a ring N atom;

the cycloalkyl in (12) or (13) is optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-4}$ alkyl, $-CF_3$, $-O-C_{1-4}$ alkyl, or $-OCF_3$; and

the phenyl in (14) or (15) is optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, $-CF_3$, or $-OCF_3$;

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A tenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) $-CO_2R^a$, (2) $-C(=O)N(R^a)R^b$, (3) $-C(=O)-N(R^a)-(CH_2)_{2-3}-OR^b$, (4) $-N(R^a)C(=O)R^b$, (5) $-N(R^a)SO_2R^b$, (6) -HetK, (7) -C(=O)-HetK, (8)

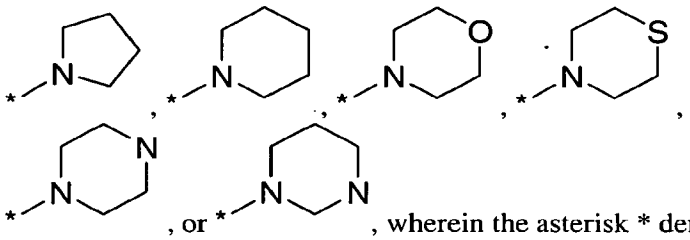
-C(=O)N(R^a)-(CH_2)$_{0-1}$-(C_{3-6} cycloalkyl), wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -CF_3, -O-C_{1-6} alkyl, or -OCF_3, or (9) -C(=O)N(R^a)-CH_2-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -O-C_{1-6} alkyl, -CF_3, -OCF_3, or halogen; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An aspect of the tenth embodiment is a compound of Formula I, or a pharmaceutically accetpable salt thereof, wherein:

wherein HetK is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or oxo; and with the proviso that when HetK is attached to the rest of the compound via the -C(=O)- moiety, the HetK is attached to the -C(=O)- via a ring N atom;

and all other variables are as defined in the tenth embodiment.

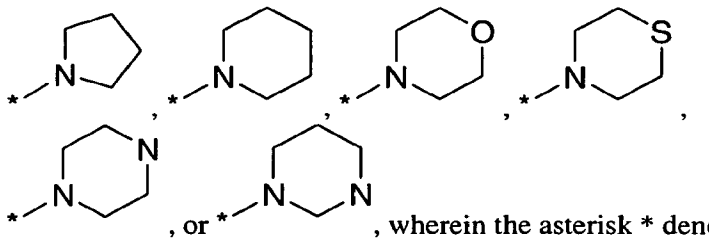
An eleventh embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) -CO_2H, (2) -C(=O)-O-C_{1-4} alkyl, (3) -C(=O)NH_2, (4) -C(=O)NH-C_{1-4} alkyl, (5) -C(=O)N(C_{1-4} alkyl)$_2$, (6) -C(=O)-NH-(CH_2)$_{2-3}$-O-C_{1-4} alkyl, (7) -C(=O)-N(C_{1-4} alkyl)-(CH_2)$_{2-3}$-O-C_{1-4} alkyl, (8) -NHC(=O)-C_{1-4} alkyl, (9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl, (10) -$NHSO_2$-C_{1-4} alkyl, (11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl, (12) -C(=O)-HetK, wherein HetK is:



, or , wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-(CH_2)$_{0-1}$-(C_{3-6} cycloalkyl), (14) -C(=O)N(C_{1-4} alkyl)-(CH_2)$_{0-1}$-(C_{3-6} cycloalkyl), (15) -C(=O)NH-CH_2-phenyl, or (16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A twelfth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is: (1) -C(=O)-O-C_{1-3} alkyl, (2) -C(=O)NH-C_{1-3} alkyl, (3) -C(=O)N(C_{1-3} alkyl)$_2$, (4) -C(=O)-N(C_{1-3} alkyl)-(CH_2)$_2$-O-C_{1-3} alkyl, (5) -N(C_{1-3} alkyl)C(=O)-C_{1-3} alkyl, (6) -N(C_{1-3} alkyl)SO_2-C_{1-3} alkyl, (7) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(8) -C(=O)NH-(CH2)0-1-(cyclopropyl), (9) -C(=O)NH-(CH2)0-1-(cyclobutyl), (10) -C(=O)N(C1-3 alkyl)-(CH_2)$_{0-1}$-cyclopropyl, (11) -C(=O)N(C_{1-3} alkyl)-(CH_2)$_{0-1}$-cyclobutyl, (12) -C(=O)NH-CH_2-phenyl, or (13) -C(=O)N(C_{1-3} alkyl)-CH_2-phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A thirteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is:

(1) -H,

(2) -C_{1-4} alkyl,

(3) -C_{3-6} cycloalkyl optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, or -O-C_{1-4} haloalkyl,

(4) -(CH_2)$_{1-2}$-C_{3-6} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, or -O-C_{1-4} haloalkyl,

(5) -(CH_2)$_{1-2}$-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} alkylene-O-C_{1-4} alkyl, -C_{1-4} haloalkyl, or -O-C_{1-4} haloalkyl, or

(6) -(CH_2)$_{1-2}$-HetD;

and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An aspect of the thirteenth embodiment is a compound of Formula I, or a pharmaceutically accetpable salt thereof, wherein: HetD is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or hydroxy; and all other variables are as defined in the tenth embodiment.

A fourteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is: (1) -H, (2) -C_{1-4} alkyl, (3) -C_{3-6} cycloalkyl, (4)

-CH_2-C_{3-6} cycloalkyl, or (5) -CH_2-phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A fifteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is: (1) -H, (2) -C_{1-4} alkyl, (3) cyclopropyl, (4) cyclobutyl, (5) -CH_2-cyclopropyl, (6) -CH_2-cyclobutyl, or (5) -CH_2-phenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

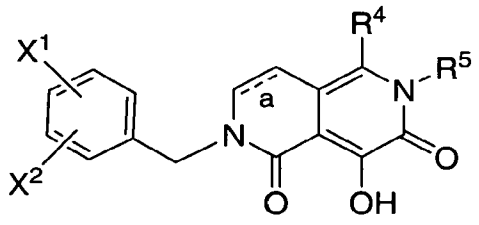
A sixteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^5 is -H; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A seventeenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are both -H; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An eighteenth embodiment of the present invention is a compound of Formula I, wherein each R^a and R^b is independently H or C_{1-3} alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A nineteenth embodiment of the present invention is a compound of Formula I, wherein each R^a and R^b is independently H or methyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

A first class of the present invention includes compounds of Formula II, and pharmaceutically acceptable salts thereof:



(II)

wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

X^1 and X^2 are each independently:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -O-C_{1-6} alkyl,

(4) -C_{1-6} haloalkyl,
(5) -O-C_{1-6} haloalkyl,
(6) halogen,
(7) -CN,
(8) -$N(R^a)R^b$,
(9) -$C(=O)N(R^a)R^b$,
(10) -$S(O)_nR^a$, wherein n is an integer equal to zero, 1, or 2,
(11) -$N(R^a)SO_2R^b$,
(12) -$N(R^a)SO_2N(R^a)R^b$,
(13) -$N(R^a)C(=O)R^b$,
(14) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$,
(15) -HetA,
(16) -C(=O)-HetA, or
(17) HetB;

wherein each HetA is independently a C_{4-5} azacycloalkyl or a C_{3-4} diazacycloalkyl, either of which is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-6} alkyl; and with the proviso that when HetA is attached to the rest of the compound via the -C(=O)- moiety, the HetA is attached to the -C(=O)- via a ring N atom; and

each HetB is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

R^4 is:

(1) -CO_2R^a,
(2) -$C(=O)N(R^a)R^b$,
(3) -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b,
(4) -$N(R^a)C(=O)R^b$,
(5) -$N(R^a)SO_2R^b$,
(6) -HetK,
(7) -C(=O)-HetK,

(8) -C(=O)N(R^a)-(CH_2)$_{0-1}$-(C_{3-6} cycloalkyl), wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -CF_3, -O-C_{1-6} alkyl, or -OCF_3, or

(9) -C(=O)N(R^a)-CH_2-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -O-C_{1-6} alkyl, -CF_3, -OCF_3, or halogen;

wherein HetK is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or oxo; and with the proviso that when HetK is attached to the rest of the compound via the -C(=O)- moiety, the HetK is attached to the -C(=O)- via a ring N atom;

R^5 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{3-6} cycloalkyl,
(4) -CH_2-C_{3-6} cycloalkyl, or
(5) -CH_2-phenyl;

each R^a is independently H or C_{1-6} alkyl; and

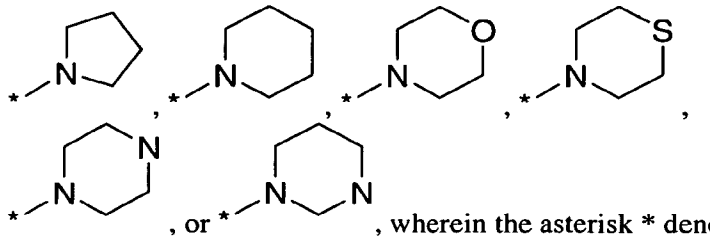
each R^b is independently H or C_{1-6} alkyl.

A sub-class of the first class includes compounds of Formula II, and pharmaceutically acceptable salts thereof, wherein

X^1 and X^2 are each independently: (1) -H, (2) -C_{1-4} alkyl, (3) -C_{1-4} haloalkyl, (4) -O-C_{1-4} alkyl, (5) halogen, (6) -CN, (7) -SO_2H, or (8) -SO_2-C_{1-4} alkyl;

R^4 is: (1) -CO_2H, (2) -C(=O)-O-C_{1-4} alkyl, (3) -C(=O)NH_2, (4) -C(=O)NH-C_{1-4} alkyl, (5) -C(=O)N(C_{1-4} alkyl)$_2$, (6) -C(=O)-NH-(CH_2)$_{2-3}$-O-C_{1-4} alkyl, (7) -C(=O)-N(C_{1-4} alkyl)-(CH_2)$_{2-3}$-O-C_{1-4} alkyl, (8) -NHC(=O)-C_{1-4} alkyl, (9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl, (10) -$NHSO_2$-C_{1-4}

alkyl, (11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl, (12) -C(=O)-HetK, wherein HetK is:

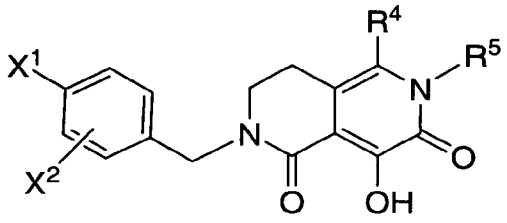


, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (15) -C(=O)NH-CH_2-phenyl, or (16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

R^5 is: (1) -H, (2) -C_{1-4} alkyl, (3) -C_{3-6} cycloalkyl, (4) -CH_2-C_{3-6} cycloalkyl, or (5) -CH_2-phenyl.

A second class of the present invention includes compounds of Formula III, and pharmaceutically acceptable salts thereof:



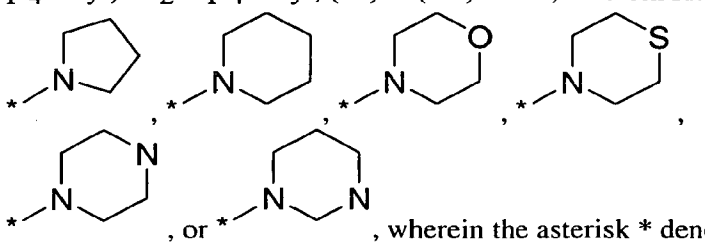
(III)

wherein:

X^1 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, or (5) methoxy;

X^2 is: (1) -H, (2) bromo, (3) chloro, (4) fluoro, (5) methoxy, (6) -C_{1-4} alkyl, (7) -CF_3, (8) -O-C_{1-4} alkyl, (9) -OCF_3, (10) -CN, or (11) -SO_2(C_{1-4} alkyl);

R^4 is: (1) -CO_2H, (2) -C(=O)-O-C_{1-4} alkyl, (3) -C(=O)NH_2, (4) -C(=O)NH-C_{1-4} alkyl, (5) -C(=O)N(C_{1-4} alkyl)$_2$, (6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl, (7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl, (8) -NHC(=O)-C_{1-4} alkyl, (9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl, (10) -$NHSO_2$-C_{1-4} alkyl, (11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl, (12) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl), (15) -C(=O)NH-CH_2-phenyl, or (16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

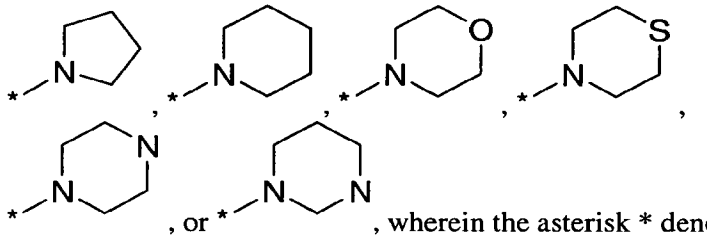
R^5 is: (1) -H, (2) -C_{1-4} alkyl, (3) cyclopropyl, (4) cyclobutyl, (5) -CH_2-cyclopropyl, (6) -CH_2-cyclobutyl, or (5) -CH_2-phenyl.

A sub-class of the second class includes compounds of Formula III, and pharmaceutically acceptable salts thereof, wherein:

X^1 is fluoro;

X^2 is -H;

R^4 is: (1) -C(=O)-O-C_{1-3} alkyl, (2) -C(=O)NH-C_{1-3} alkyl, (3) -C(=O)N(C_{1-3} alkyl)$_2$, (4) -C(=O)-N(C_{1-3} alkyl)-$(CH_2)_2$-O-C_{1-3} alkyl, (5) -N(C_{1-3} alkyl)C(=O)-C_{1-3} alkyl, (6) -N(C_{1-3} alkyl)SO_2-C_{1-3} alkyl, (7) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(8) -C(=O)NH-$(CH_2)_{0-1}$-(cyclopropyl), (9) -C(=O)NH-$(CH_2)_{0-1}$-(cyclobutyl), (10) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclopropyl, (11) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl, (12) -C(=O)NH-CH_2-phenyl, or (13) -C(=O)N(C_{1-3} alkyl)-CH_2-phenyl; and

R^5 is -H.

Another embodiment of the present invention is a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of the compounds set forth in Examples 1 to 12 below.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising an effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(e) A pharmaceutical combination which is (i) a compound of Formula I and (ii) an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents; wherein the compound of Formula I and the HIV infection/AIDS treatment agent are each employed in an amount that renders the combination effective for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS.

(f) The combination of (e), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

(g) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(h) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(i) The method of (h), wherein the compound of Formula (I) is administered in combination with an effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(k) The method of (j), wherein the compound is administered in combination with an effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

(l) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more HIV/AIDS treatment agents selected from HIV/AIDS antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "alkylene" refers to any linear or branched chain alkylene group (or alternatively "alkanediyl") having a number of carbon atoms in the specified range. Thus, for example, "-C_{1-6} alkylene-" refers to any of the C_1 to C_6 linear or branched alkylenes. A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-. Also of interest is the alkylene -$CH(CH_3)$-.

The terms "cycloalkyl" refers to any cyclic ring of an alkane having a number of carbon atoms in the specified range. Thus, for example, "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "haloalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms has been replaced with a halogen (i.e., F, Cl, Br and/or I). Thus, for example, "C_{1-6}

haloalkyl" (or "C_1-C_6 haloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "C_{4-7} azacycloalkyl" (or "C_4-C_7 azacycloalkyl") means a saturated cyclic ring consisting of one nitrogen and from four to seven carbon atoms (i.e., pyrrolidinyl, piperidinyl, azepanyl, or octahydroazocinyl).

The term "C_{3-6} diazacycloalkyl" (or "C_3-C_6 diazacycloalkyl") means a saturated cyclic ring consisting of two nitrogens and from three to six carbon atoms (e.g., imidazolidinyl, pyrazolidinyl, or piperazinyl).

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" means the ring can contain 1, 2, 3 or 4 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. Thus, for example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" is intended to include as aspects thereof, heterocyclic rings containing 2 to 4 heteroatoms, 3 or 4 heteroatoms, 1 to 3 heteroatoms, 2 or 3 heteroatoms, 1 or 2 heteroatoms, 1 heteroatom, 2 heteroatoms, and so forth.

When any variable (e.g., R^a, R^b, or HetA) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "substituted" (e.g., as in "is optionally substituted with from 1 to 5 substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed. Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., aryl, a heteroaromatic ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound.

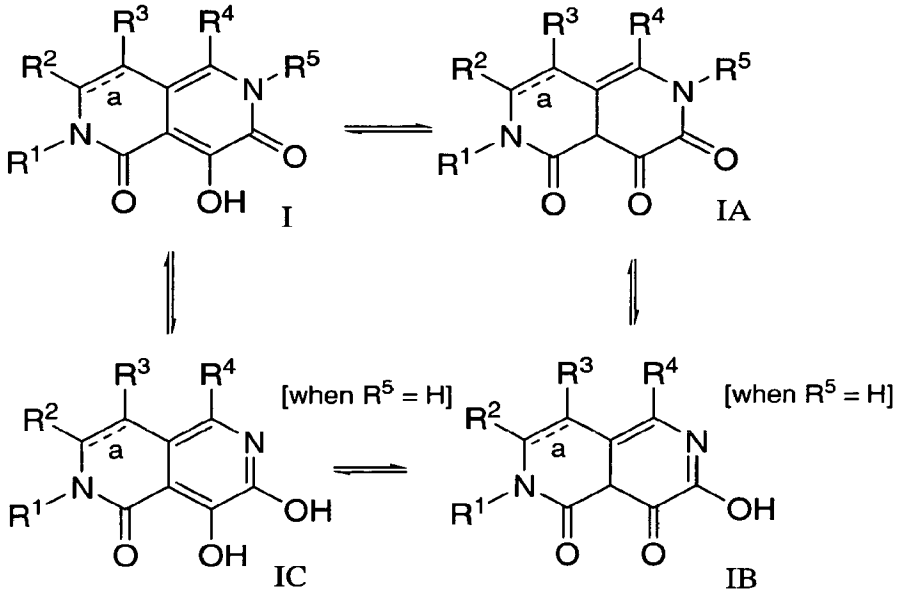
Any of the various carbocyclic and heterocyclic rings and ring systems defined herein may be attached to the rest of the compound at any ring atom (i.e., any carbon atom or any heteroatom) provided that a stable compound results. Suitable 5- or 6-membered heteroaromatic rings include, for example, pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. The foregoing are representative of heteroaromatics defined by HetB and HetL, and

included in the definitions of HetC and HetD. Suitable heteroaryls consisting of an aryl fused with a 5- or 6-membered heteroaromatic ring include, for example, benzopiperidinyl, benzisoxazolyl, benzoxazolyl, chromenyl, quinolinyl, isoquinolinyl, cinnolinyl, and quinazolinyl. The foregoing are representative of fused bicyclic heteroaryls included in the definition of HetC and of fused aryl in part (A) of the definition of R^J. Suitable 4- to 7-membered saturated heterocyclics include, for example, azetidinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, thiadiazepanyl, dithiazepanyl, azepanyl, diazepanyl, thiadiazinanyl, tetrahydropyranyl, tetrahydrothiopyranyl, and dioxanyl. The foregoing are representative of saturated heterocyclics defined by HetK and included in the definition of HetD.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

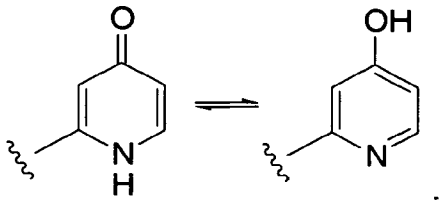
As a result of the selection of substituents and substituent patterns, certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

As would be recognized by one of ordinary skill in the art, certain of the compounds of the present invention can exist as tautomers, such as the following:



For the purposes of the present invention a reference herein to a compound of Formula I, II, or III is a reference to the compound per se, or to any one of its tautomers per se, or to mixtures of two or more tautomers.

In instances where a hydroxy (-OH) substituent(s) is(are) permitted on a heteroaromatic ring and keto-enol tautomerism is possible, it is understood that the substituent might in fact be present, in whole or in part, in the keto form, as exemplified here for a hydroxypyridinyl substituent:



Compounds of the present invention having a hydroxy substituent on a carbon atom of a heteroaromatic ring are understood to include compounds in which only the hydroxy is present, compounds in which only the tautomeric keto form (i.e., an oxo substitutent) is present, and compounds in which the keto and enol forms are both present.

The compounds of the present inventions are useful in the inhibition of HIV integrase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the prevention, treatment or the delay in the onset of consequent pathological conditions such as AIDS. Preventing AIDS, treating AIDS, delaying the onset of AIDS, or preventing or treating infection by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise

undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV infection or AIDS), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or prodrug and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combining the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being prevented. The term also includes herein the amount of active compound sufficient to inhibit HIV integrase and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

For the purpose of inhibiting HIV integrase, preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention, optionally in the form of a salt, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age,

body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention is also directed to use of the HIV integrase inhibitor compounds of the present invention with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more HIV/AIDS antivirals, imunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS, such as those disclosed in Table 1 of WO 01/38332 or in the Table in WO 02/30930. Suitable HIV/AIDS antivirals for use in combination with the compounds of the present invention include, for example, HIV protease inhibitors (e.g., indinavir, atazanavir, lopinavir optionally with ritonavir, saquinavir, or nelfinavir), nucleoside HIV reverse transcriptase inhibitors (e.g., abacavir, lamivudine (3TC), zidovudine (AZT), or tenofovir), and non-nucleoside HIV reverse transcriptase inhibitors (e.g., efavirenz or nevirapine). It will be understood that the scope of combinations of the compounds of this invention with HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the foregoing substances or to the list in the above-referenced Tables in WO 01/38332 and WO 02/30930, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS. The HIV/AIDS antivirals and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, 57th edition, Thomson PDR, 2003. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

Abbreviations used in the instant specification, particularly the in the Schemes and Examples, include the following:

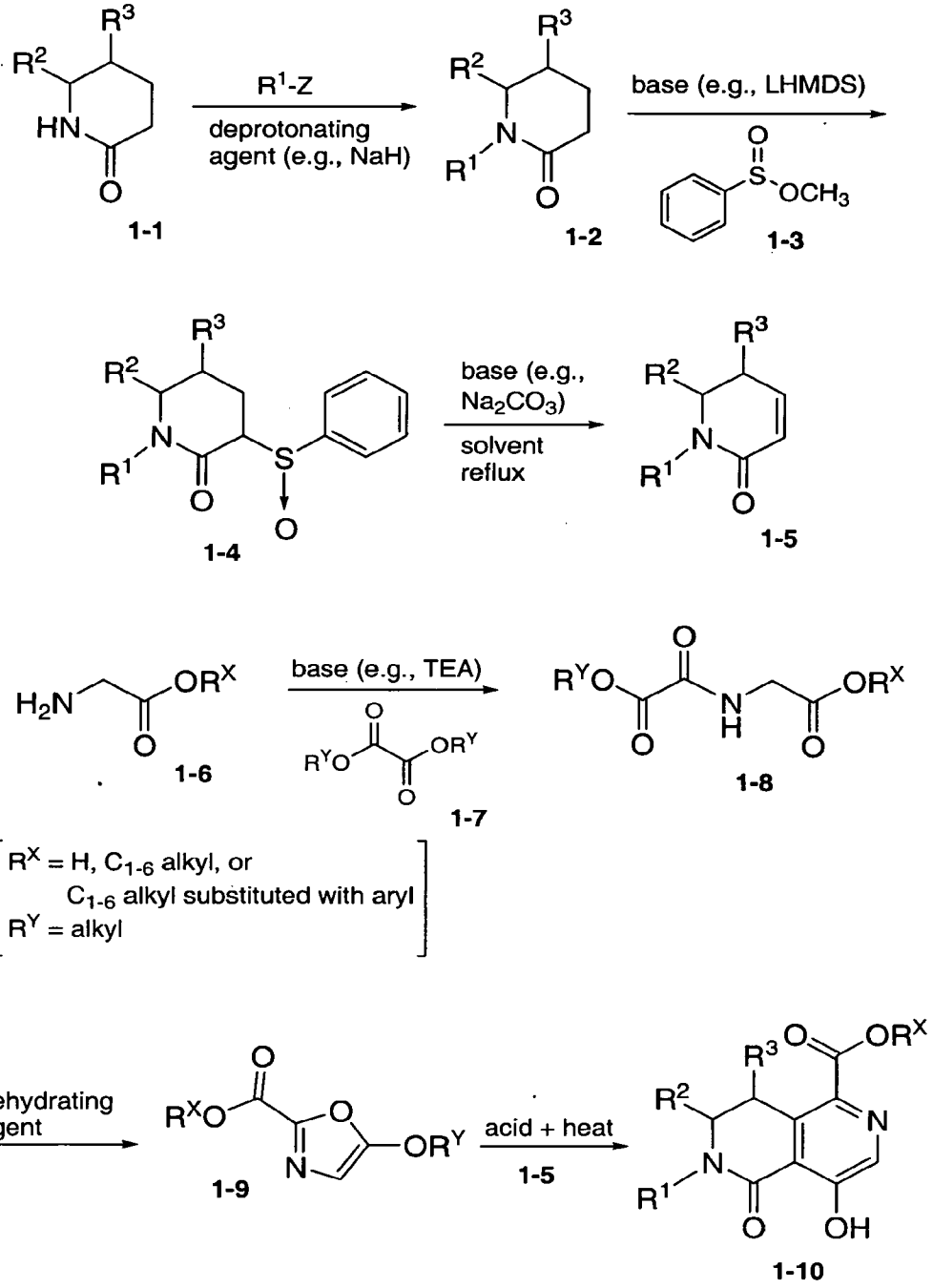
Ac = acetyl
AIDS = acquired immunodeficiency syndrome
AIBN = 2,2-azobisisobutyronitrile
ARC = AIDS related complex
BOP = benzotriazol-1-yloxytris-(dimethylamino)phosphonium
DMF = N,N-dimethylformamide
DMSO = dimethylsulfoxide
ES MS = electrospray mass spectroscopy
EtOAc = ethyl acetate
HIV = human immunodeficiency virus
HOAc = acetic acid

HPLC = high performance liquid chromatography
LHMDS = lithium hexamethyldisilazide
mCPBA = meta-chloroperbenzoic acid
Me = methyl
MeOH = methanol
NBS = N-bromosuccinimide
NMR = nuclear magnetic resonance
TEA = triethylamine
TFA = trifluoroacetic acid
THF = tetrahydrofuran

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

Scheme 1 depicts a method for preparing 5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate intermediates useful for making compounds of the present invention. In the scheme, lactam **1-1** can be alkylated with an appropriate alkyl halide to give **1-2**, using methods as described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 377-379. Piperidin-2-one **1-2** can be converted to the corresponding dihydropyridinone compound **1-5** following the two step procedure set forth in Meyers et al., *Tett. Lett.* 1995, 36: 7051-7054, wherein the lactam can be treated with base and methyl benzene sulfinate to give intermediate **1-4**, which can then be treated by heating in a high boiling solvent (e.g., toluene) and optionally in the presence of base to effect the elimination to **1-5**. Separately, oxazoles of the type **1-9** can readily be prepared by acylating amino acid ester **1-6** with an oxylate ester **1-7** in the presence of base to afford acylated compound **1-8**, which can then be cyclized and dehydrated (using, e.g., P_2O_5) in the manner described in Krapcho et al. *J. Heterocyclic Chem.* 1995, 32, 1693-1702 to afford oxazole **1-9**. Diels-Alder reaction of **1-9** and **1-5**, optionally but preferably in the presence of acid, will then provide the desired napthyridine intermediate **1-10**.

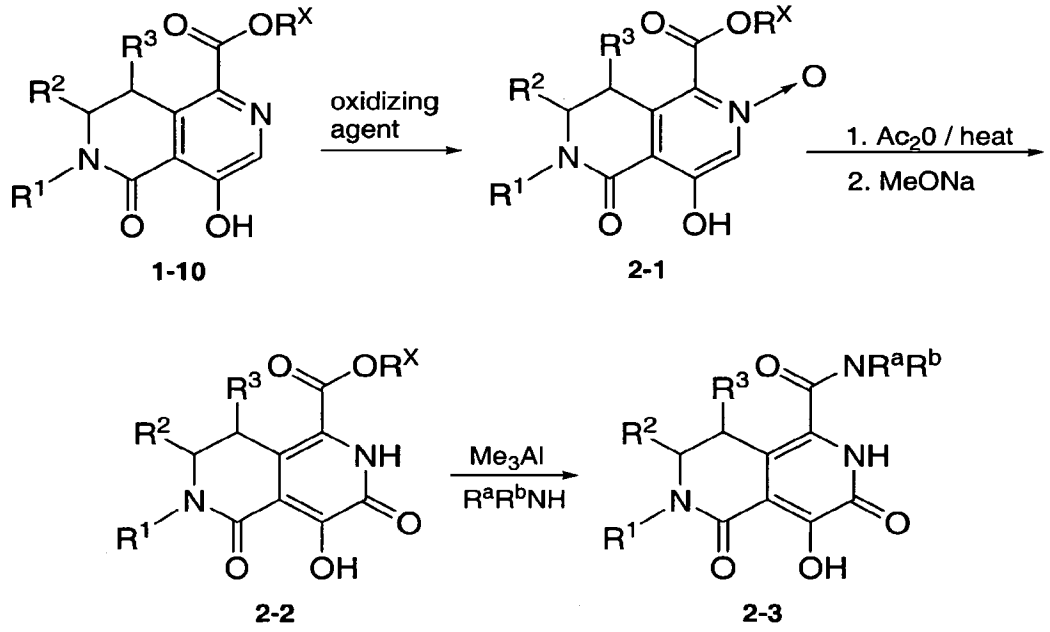
SCHEME 1



Scheme 2 depicts a method for preparing naphthyridine carboxylates and carboxamides embraced by the present invention from naphthyridine intermediate **1-10**, wherein the intermediate **1-10**

is contacted with a suitable oxidizing agent (e.g., hydrogen peroxide or mCPBA) to obtain N-oxide **2-1**, which can then be treated as described Suzuki et al. *J.Med. Chem.* 1992, 35, 4045-4053 with acetic anhydride to effect the rearrangement to the O-acylated intermediate, and then treated with a nucleophile (e.g., an alkoxide such as NaOMe) to afford the desired dioxohexahydro-2,6-naphthyridine-1-carboxylate **2-2**. The alkyl carboxylate **2-2** can then be further treated with an appropriate amine and trimethylaluminum in the manner described in Evans et al., *J. Am. Chem. Soc.* 1990, 112: 7001 to give the desired alkyl carboxamide **2-3**.

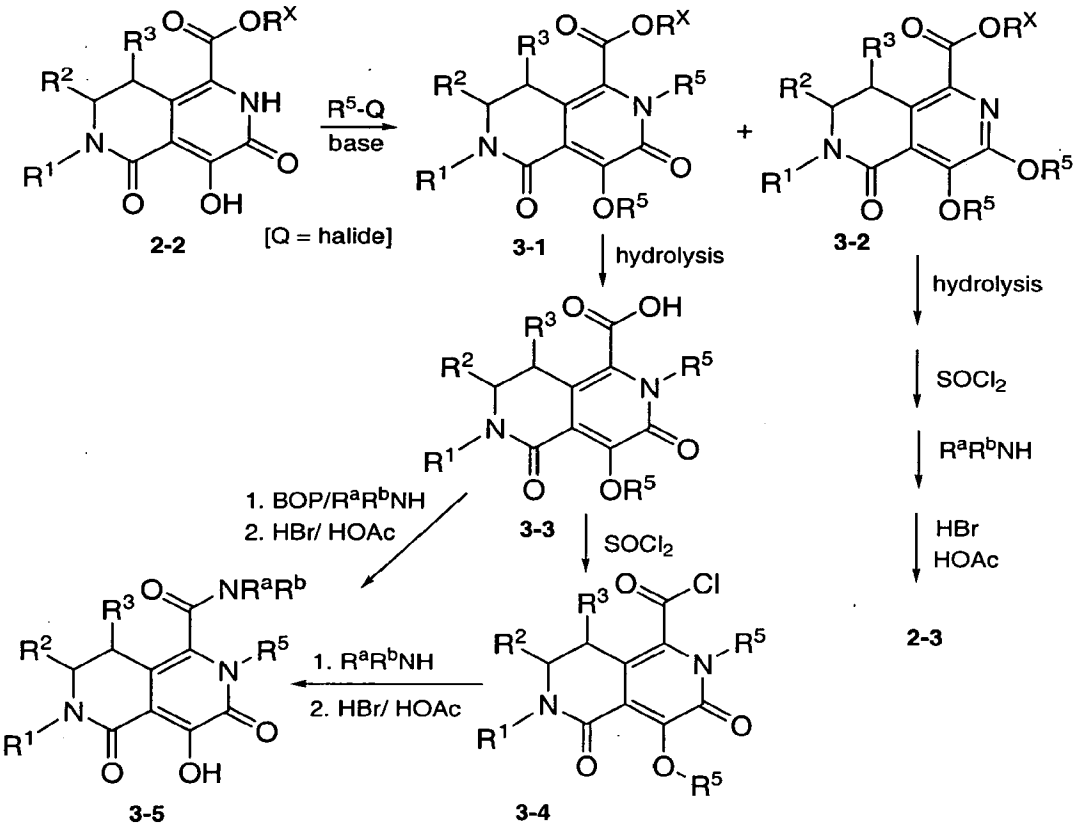
SCHEME 2



Scheme 3 depicts an alternative method for preparing naphthyridine carboxamides **2-3** and analogs in which the R^5 substituent is other than H. The intermediate **2-2** can be alkylated with an alkylating agent (e.g., an alkyl halide or an alkyl sulfate such as dimethyl sulfate) using a suitable base (e.g., an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3, an alkali metal hydride such as NaH, or a metal alkoxide such as $Mg(OMe)_2$) to give a mixture of N- and O-alkylated products **3-1** and **3-2**, similar to the method described in T. Ukita et.al., *Chem. Pharm. Bull.* 2000, 48 (4): 589-591. Analogs possessing a non-H R^5 substituent can also be prepared by hydrolysis of the N-alkylated product **3-1** with a nucleophile such as hydroxide to afford the acid **3-3**, followed by conversion to the acid chloride **3-4** using a suitable agent like thionyl chloride or oxalyl chloride/catalytic DMF, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 388.

The acid **3-3** can be coupled with an amine using a peptide coupling reagent such as BOP, or, alternatively, the acid chloride **3-4** can be treated directly with an amine to give the amide. The O-alkyl groups can then be removed under acidic conditions (e.g., using a strong acid like HBr in a suitable solvent like acetic or propionic acid, or using p-toluene sulfonic acid, or a reagent like BBr_3) to give **3-5**, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 384. A similar sequence of hydrolysis, acid chloride formation, coupling and de-protection, starting from the bis-O-alkylated compound **3-2**, can allow the preparation of compounds **2-3**.

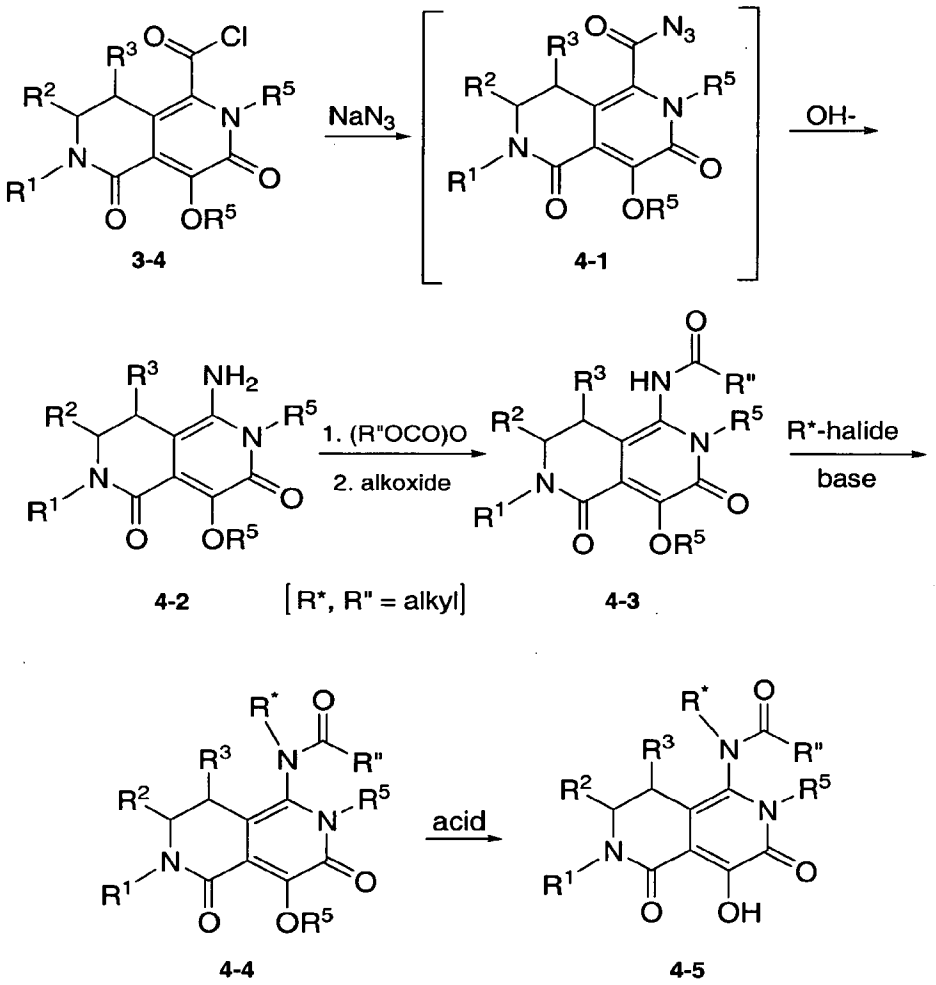
SCHEME 3



Scheme 4 depicts a method for preparing compounds of the invention in which the R^4 group is linked to the parent template via a nitrogen-carbon bond. Acid chloride 3-4 can be treated with sodium azide to give the acyl azide, which will undergo Curtius rearrangement followed by hydrolysis to the amine **4-2**, similar to the method described in R.J. Borchis et.al. *J. Med. Chem.* (1981), 24, 1518-1521. The amine may then be acylated or sulfonylated with the appropriate agent like an acyl or sulfonyl anhydride or acyl or sulfonyl chloride to give the mono or bis N-acyl or N-sulfonylated intermediate,

which can then be converted to product **4-3** by using a suitable nucleophile like sodium methoxide or sodium hydroxide. The amine can further be modified by alkylation with a suitable alkyl halide under the influence of a base (e.g., Cs_2CO_3 or K_2CO_3, using a method similar to that described in A. Nadin, et.al. *J. Org. Chem.* (2003), 68(7), 2844-2852, to give compounds **4-4**. The O-alkyl group can then be removed with a strong acid like HBr to give **4-5**.

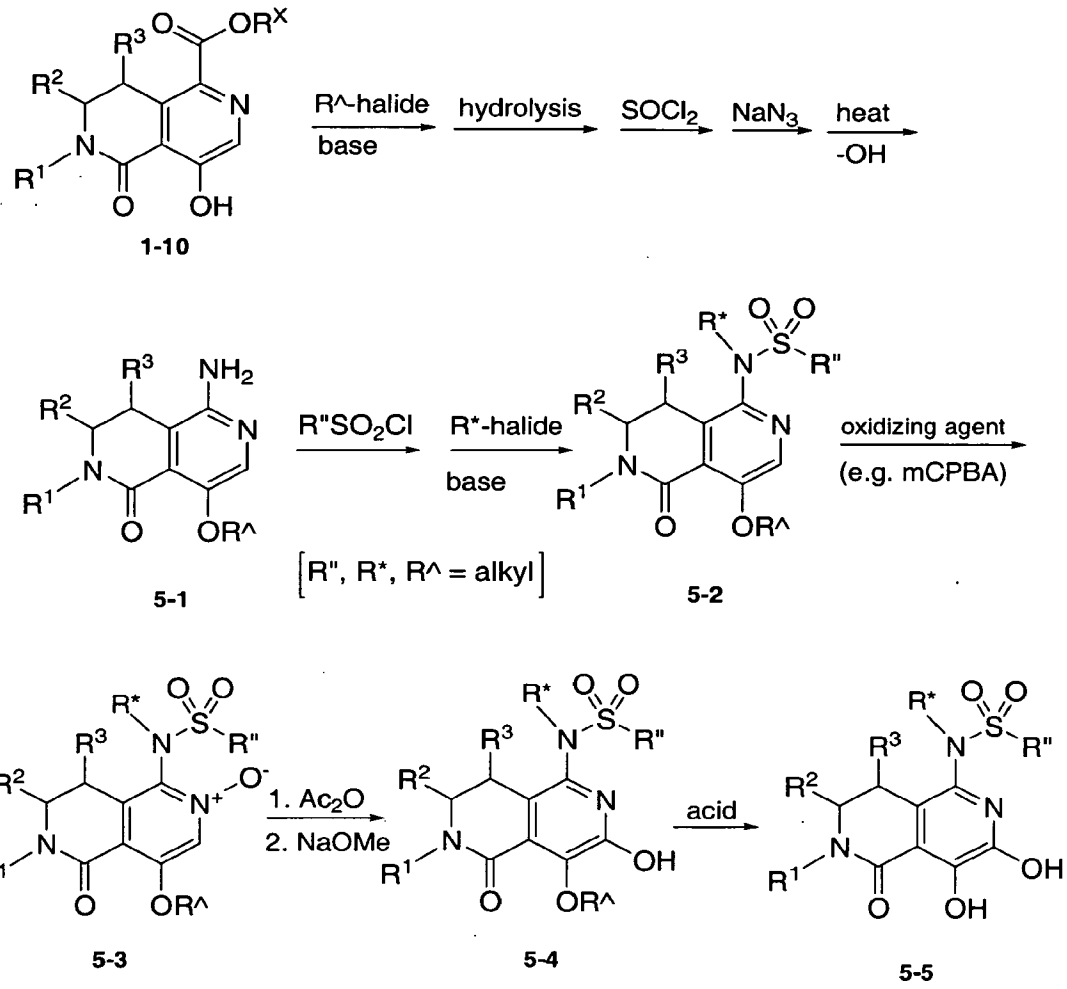
SCHEME 4



Scheme 5 depicts an alternative sequence of transformations similar to those described in the above schemes. Starting with the intermediate **1-10**, O-alkylation, hydrolysis of the ester to the acid, acid chloride formation, acyl azide formation, Curtius rearrangement and hydrolysis give the intermediate **5-1**, which can be derivatized with various acyl or sulfonyl halides, and then alkylated to

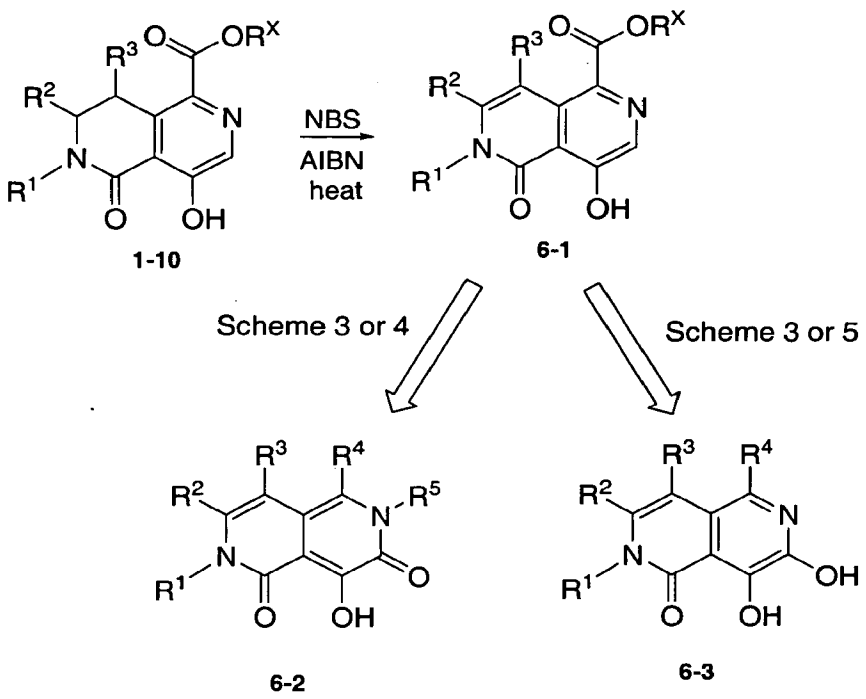
give **5-2**. N-oxide formation, similar to that described in M. Adamczyk, *Tetrahedron* (2002) 58, 6951-6963, followed by rearrangement in acetic anhydride and hydrolysis will give **5-4**, and cleavage of the O-alkyl group in acid will afford **5-5**.

SCHEME 5



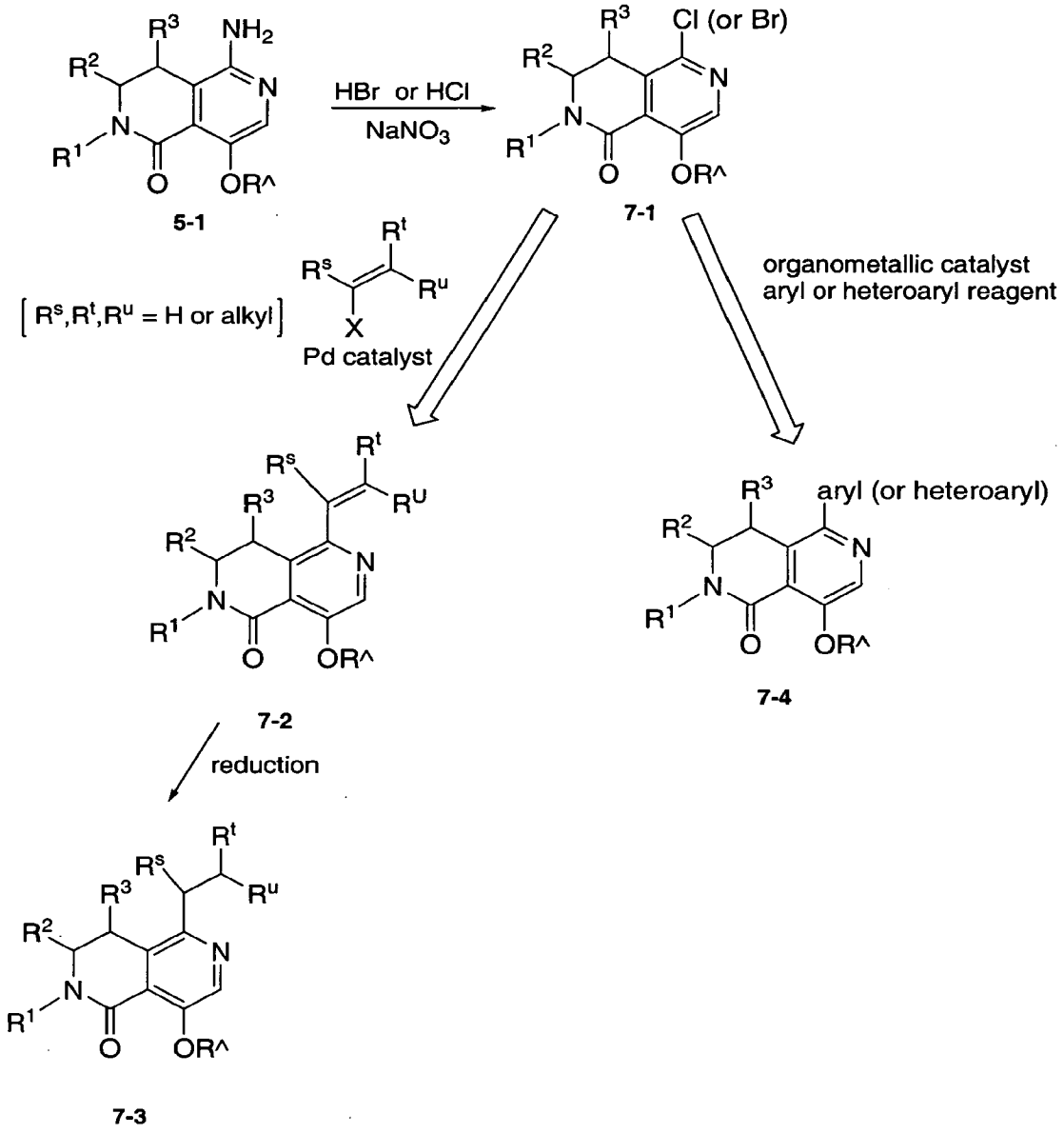
Scheme 6 depicts a route to compounds containing a double bond in the "a" position. These analogs can be prepared from treatment of an intermediate like **1-10** with a brominating agent (e.g., NBS) followed by elimination to give the double bond, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 914. The intermediate **6-1** can then be taken through a series of transformations as previously outlined to give products **6-2** and **6-3**.

SCHEME 6



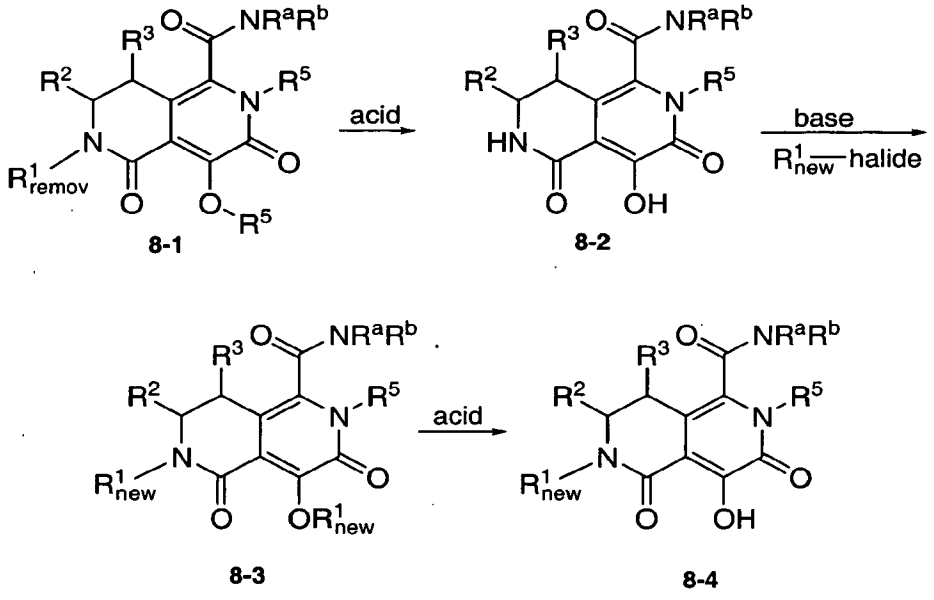
Scheme 7 shows methods that can be used to prepare analogs in which R^4 is attached by a carbon-carbon bond. The amine **4-2** or **5-1** can be converted to the halide **7-1**, using methods described in A. Bouillon et.al. *Tetrahedron* 58 (14) 2885-2890 (2002), which will allow for carbon-carbon bond formation. Treatment of the halide with a palladium catalyst and vinyl halide, for example, using methods developed by R. F. Heck (M. Schlosser, Organometallics in Synthesis, a Manual 2nd ed. John Wiley and Sons, Ltd. NY 2002, pp 1169) can provide intermediate **7-2**, which can be reduced to the alkyl analog **7-3**. Similarly, treatment of the halide with an organometallic catalyst such as zinc or palladium and an aryl or heteroaryl boronic acid, an aryl or heteroaryl tin reagent, or an aryl and heteroaryl halide will afford the product **7-4** Such transformations are well known in the art and are described, for example, in J.J. Li, G.W.Gribble Palladium in Heterocyclic Chemistry, Pergamon Press NY 2000. Compounds **7-3** and **7-4** can then be taken through the sequence of steps elaborated in previous schemes to afford additional compounds of the present invention.

SCHEME 7



Scheme 8 depicts a method for preparing analogs with R^1 substituents from starting substrate **8-1** with a removable R^1 group. Substrate **8-1**, containing an R^1 functional group readily removable from an amide moiety (e.g., p-methoxybenzyl, 3,4- or 2,4-bismethoxybenzyl, allyl, or tosyl), can be prepared by coupling a suitable acid **3-3** or acid chloride **3-4** with an amine (see Scheme 3), and can be de-protected with a strong acid like p-toluene sulfonic acid in a manner similar to the method described in W.M. Kan et.al., *Tetrahedron* 2000, 44: 1039-1041 to give intermediate **8-2**. Deprotected

compound **8-2** can then be bis-alkylated with a suitable alkyl halide using a base (e.g., NaH) to give the N,O-alkylated intermediate **8-3**. Removal of the O-alkyl group with strong acid (e.g., HBR in a solvent such as acetic or propionic acid) will then afford the product **8-4**.

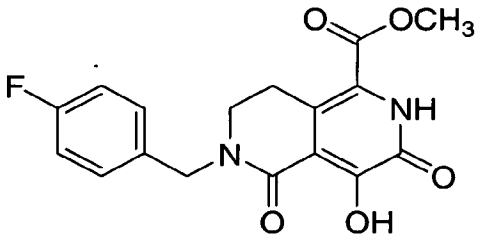


8-1 **8-2** **8-3** **8-4**

The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

Methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate



Step 1: 1-(4-Fluorobenzyl)piperidine-2-one

To a suspension of sodium hydride (2.4 g, 0.1 mol) in anhydrous THF (400 mL) was added piperidine-2-one (9.0 g, 90 mmol) in anhydrous THF (20 mL) over 10 minutes. After 20 minutes, the resultant thick slurry was treated with 4-fluorobenzyl bromide (18.9 g, 99.9 mmol). The reaction mixture was refluxed overnight. The resultant mixture was cooled to 0 °C and treated with H_2O (10 mL) cautiously. The mixture was stirred for 10 minutes and concentrated under vacuum. The residue was

partitioned between ethyl acetate (300 mL) and H_2O. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The residual oil was subjected to column chromatography on silica gel eluting with 50 % - 70 % ethyl acetate in hexanes. The appropriate fractions were combined and concentrated to afford the benzylated piperidinone as a white solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J*= 8.7 Hz, 5.4 Hz, 2H), 7.00 (t, *J*=8.7 Hz, 2H), 4.56 (s, 2H), 3.18 (t, *J*=6 Hz, 2H), 2.46 (t, *J*=6 Hz, 2H), 1.79 (m, 4H).

Step 2: 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one

To a cooled (0 °C) solution of 1-(4-fluorobenzyl)piperidine (5.0g, 24.1 mmol) in anhydrous THF (100 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 53 mL, 53 mmol) dropwise, and the solution was stirred for one half hour. The solution was treated with methyl benzene sulfinate (5.65g, 36.1 mmol) in anhydrous THF (3 mL) dropwise. After 30 minutes at 0 °C, the resultant mixture was quenched with water and partitioned between 10% $KHSO_4$ and $CHCl_3$, the layers separated and the aqueous extracted several more times with $CHCl_3$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to afford 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one as a waxy solid that was taken on to the next step. ES MS M+1 = 332

Step 3: 1-(4-Fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one

To a solution of 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one (0.37 g, 1.11 mmol) in toluene (15 mL) was added solid Na_2CO_3 (2g, 18.8 mmol). The reaction mixture was refluxed for about 6 hours. The resultant solution was filtered and concentrated under vacuum and the residue chromatographed on silica eluting with a gradient of 0-40% EtOAc/Hexanes to give the product as colorless glass.
^{1}HNMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.01 (m, 2H), 6.56 (dt, *J*=9.9 Hz, 4.2 Hz, 1H), 6.00 (dt, *J*=9.7 Hz, 1.8 Hz, 1H), 4.59 (s, 2H), 3.32 (t, *J*=7.2 Hz, 2H), 2.33 (m, 2H).

Step 4: Methyl[(2-methoxy-2-oxoethyl)amino](oxo)acetate

To a cooled (0 °C) solution of the glycine methyl ester (30.0 g, 0.24 mol) in methylene chloride (500 mL) was added triethylamine (50.8 g, 0.50 mol). Methyl oxalyl chloride (29.3 g, 0.24 mol) was carefully added dropwise. The reaction solution warmed to room temperature and stirred overnight. The product mixture was partitioned between H_2O and methylene chloride. The organic extract was dried with Na_2SO_4 and concentrated under vacuum to afford the title compound as a brown oil.
^{1}HNMR (400 MHz, $CDCl_3$) δ 7.59 (br, 1H), 4.14 (d, *J*=5.6 Hz, 2H), 3.93 (s, 3H), 3.79 (s, 3H). ES MS M+1 = 176

Step 5: Methyl 5-methoxy-1, 3-oxazole-2-carboxylate

To a warm (35 - 40 °C) suspension of phosphorous pentoxide (77.7 g, 109 mmol) in anhydrous acetonitrile (200 mL) was added methyl[(2-methoxy-2-oxoethyl)amino](oxo)acetate (19.19 g, 109.6 mmol). The reaction mixture was heated to 65 °C, then stirred overnight at room temperature. The product mixture was cooled to 0 °C and carefully quenched with ice and brine keeping the reaction from generating an unsuitable exotherm. The resultant mixture was extracted with ethyl acetate (600 mL). The organic extract was washed with brine, dried with Na_2SO_4, then concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 100 % CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the title compound as a light yellow solid that was used without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H). ES MS M+1 =158

Step 6: Methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

In a sealed tube, 1-(4-fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one (3.84 g, 18.7 mmol), and methyl 5-methoxy-1,3-oxazole-2-carboxylate prepared in Step 5 (2.94 g, 18.7 mmol), were combined. The reaction mixture was heated at 120 °C. After 24 hours, the resultant mixture was cooled and methanol saturated with HCl (2 mL) was added. The product mixture stirred at room temperature for 40 minutes, then was concentrated under vacuum. The residual crude material was diluted with DMSO (6.0 mL) and filtered to give the title compound.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (br, 1H), 8.39 (s, 1H), 7.31 (m, 2H), 7.06 (t, *J*=8.5 Hz, 2H), 4.72 (s, 2H), 3.94 (s, 3H), 3.50 (m, 4H). ES MS M+1 =331

Step 7: Methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide

To a solution of methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (0.509 g, 1.541 mmol) in acetic acid (2 mL) was added hydrogen peroxide (35 % wt % in H_2O, 0.262 g, 7.705 mmol). The reaction mixture was heated to 100 °C for 1 hour. The product mixture was concentrated under vacuum and purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a yellow solid.
^{1}HNMR (400 MHz, CD_3OD) δ 7.95 (s, 1H), 7.38 (dd, *J*=5.3 Hz, 8.6 Hz, 2H), 7.08 (t, *J*=8.8 Hz, 2H), 4.71 (s, 2H), 3.93 (s, 3H), 3.56 (t, *J*=6.7 Hz, 2H), 2.89 (t, *J*=6.7 Hz, 2H). ES MS M+1 = 347

Step 8: Methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

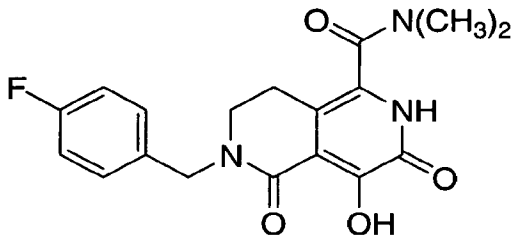
To methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (0.178 g, 0.514 mmol) was added acetic anhydride (0.157 g, 1.542 mmol) and refluxed. After 1 hour, the reaction mixture was concentrated under vacuum, then sodium methoxide (30 wt. % in methanol, 0.083 g, 1.540 mmol) was added. After stirring at room temperature for 1 hour, the product mixture was concentrated under vacuum. The residue was purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a pale yellow solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.3 Hz, 8.4 Hz, 2h), 7.06 (t, *J*=8.5 Hz, 2H), 4.71 (s, 2H), 3.93 (s, 3H), 3.46 (t, *J*=6.5 Hz, 2H), 3.32 (t, *J*=6.5 Hz, 2H).

ES MS M+1 = 347

EXAMPLE 2

6-(4-Fluorobenzyl)-4-hydroxy-*N*,*N*-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

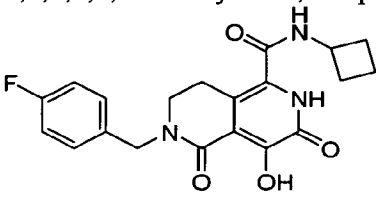
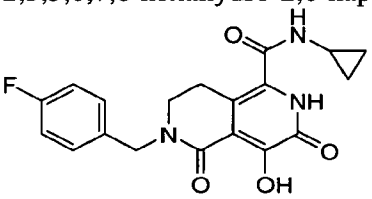
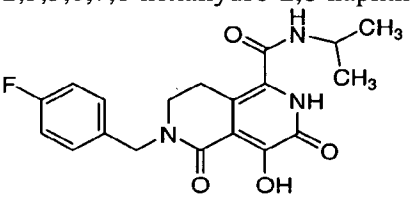


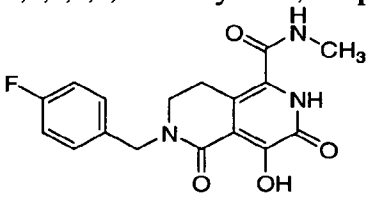
To a cooled (-10 °C) solution of dimethylamine (2M in THF, 0.002 g, 0.035 mmol) was slowly added trimethylaluminum (2M in toluene, 0.002 g, 0.035 mmol) and stirred for 30 minutes at room temperature. The reaction mixture was cooled to -10 °C and methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.004 g, 0.012 mmol, example 1 step 8) in CH_2Cl_2 (0.5 mL) was added. The reaction stirred at room temperature for 2 hours, then recooled to 0 °C. A solution of 1:1 CH_2Cl_2:0.5 N aq. HCl was added and stirred for 1 hour at room temperature. The product mixture was partitioned between CH_2Cl_2 and H_2O. The organic extract was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a light yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (dd, *J*= 5.3 Hz, 8.6 Hz, 2H), 7.09 (t, *J*=8.8 Hz, 2H), 4.74 (s, 2H), 3.50 (t, *J*=6.4 Hz, 2H), 3.05 (s, 3H), 2.96 (s, 3H), 2.67 (t, *J*=6.4 Hz, 2H) ppm. ES MS M+1 = 360

EXAMPLES 3 - 6

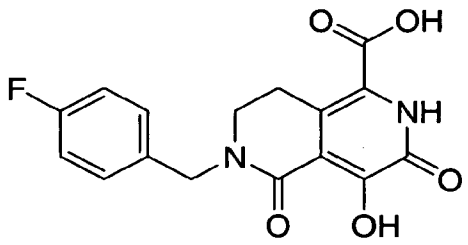
The compounds in the following table were prepared in accordance with the procedure set forth in Example 2 using the appropriate analogous starting materials.

Example	Compound	Data
3	*N*-Cyclobutyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}HNMR (400 MHz, CD_3OD) δ 7.39 (dd, *J*=5.6 Hz, 8.7 Hz, 2H), 7.09 (t, *J*=8.7 Hz, 2H), 4.74 (s, 2H), 4.39 (p, *J*=7.9 Hz, 1H), 3.49 (t, *J*=6.1 Hz, 2H), 3.06 (t, *J*=6.1 Hz, 2H), 2.32 (m, 2H), 2.04 (m, 2H), 1.78 (m, 2H) ppm. ES MS M+1 = 386
4	*N*-Cyclopropyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}HNMR (400 MHz, $CDCl_3$) δ 13.53 (br, 1H), 7.63 (br, 1H), 7.30 (dd, *J*=5.6 Hz, 8.5 Hz, 2H), 7.06 (t, *J*=8.5 Hz, 2H), 4.71 (s, 2H), 3.51 (m, 2H), 3.46 (m, 2H), 2.86 (m, 1H), 1.88 (br, 1H), 0.83 (q, *J*=5.9 Hz, 2H), 0.71 (m, 2H) ppm. ES MS M+1 = 372
5	6-(4-Fluorobenzyl)-4-hydroxy-*N*-isopropyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.7 Hz, 8.8 Hz, 2H), 7.06 (t, *J*=8.8 Hz, 2H), 6.89 (d, *J*=7.3 Hz, 1H), 4.82 (br, 1H), 4.71 (s, 2H), 4.17 (m, 1H), 3.47 (t, *J*=6.3 Hz, 2H), 3.35 (t, *J*=6.3 Hz, 2H), 1.26 (d, *J*=6.1 Hz, 6H) ppm. ES MS M+1 = 374

6	6-(4-fluorobenzyl)-4-hydroxy-N-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.08 (m, 2H), 4.73 (s, 2H), 3.48 (t, J = 6.6 Hz, 2H), 3.08 (t, J = 6.5 Hz, 2H), 2.85 (s, 3H) ppm. MS m/z 346.3 (M +1).

EXAMPLE 7

6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid



To methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (0.178 g, 0.514 mmol) in wet methanol was added N,N-dimethylamine in MeOH (4.0 eq.). The reaction mixture was put in a microwave reactor where it was heated at 130 °C for 1.5 hours, after which the reaction mixture was concentrated under vacuum. The residue was purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a solid. . Alternatively, the starting material can be treated with LiOH in 1:1:1 THF/MeOH/H_2O to give the product.

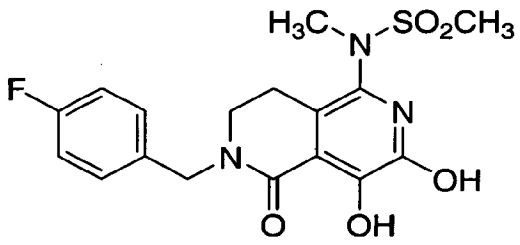
^{1}HNMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.06 (m, 2H), 4.74 (s, 2H), 3.48 (m, 2H), 3.32 (m, 2H).

ES MS M+1 = 333

EXAMPLE 8

N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-

methylmethanesulfonamide



Step 1: 1-(glycyloxy)butane chloride

To a suspension of glycine hydrochloride (10g, 89.6 mmol) in 250ml butanol under nitrogen was added thionyl chloride (45.7ml, 627 mmol) dropwise. After the addition was complete, the solution was heated at 70 °C overnight. The volatile components were removed on the roto-evaporator and the residue was suspended and evaporated from toluene three times. The resulting crude gum was dissolved in an equal weight of toluene for easy transfer and was used as is in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (bs, 3H), 4.18 (t, *J*=6.7 Hz, 2H), 4.0 (bs, 2H), 1.62 (m, 2H), 1.38 (m, 2H), 0.92 (t, *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 132.

Step 2: Butyl N-[ethoxy(oxo)acetyl]glycinate

A 1:1 by weight solution of 1-(glycyloxy)butane chloride (10g, 59.6 mmol) in toluene (10g) was treated with EtOH ((100ml), then Triethylamine (10ml, 71.6 mmol) and diethyloxalate (16.2ml, 119.3 mmol) and heated to 50 °C for three hours. . The volatile components were removed on the roto-evaporator and the residue was dissolved in $CHCl_3$, washed two times with 10% $KHSO_4$, the aqueous layer was washed two times with $CHCl_3$, the organic layers were combined, dried over Na_2SO_4, filtered and evaporated to give the crude oil, which was chromatographed on silica eluting first with 20% EtOAc/hexanes and then with 50% EtOAc/hexanes to give clean product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 4.37 (q, *J*=7.2 Hz, 2H), 4.2 (t, , *J*=6.6 Hz, 2H), 4.12 (d, *J*=5.5 Hz, 2H), 1.64 (p, *J*=6.8 Hz, 2H), 1.39 (t, *J*=7.15 Hz, 3H), 1.37 (m, buried, 2H), 0.94 (t, , *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 232

Step 3: Ethyl 5-butoxy-1,3-oxazole-2-carboxylate

A suspension of P_2O_5 (22g, 155.6 mmol) in CH_3CN (50ml) under nitrogen was warmed to 50 °C and treated with butyl N-[ethoxy(oxo)acetyl]glycinate (6g, 25.9 mmol) dissolved in 10ml CH_3CN. The mixture was heated to 65 °C for 1.5 hours, then cooled in an ice bath. Ice and brine were added to the reaction mixture, then EtOAc was added and the mixture transferred to a separatory funnel.

$CHCl_3$ was added to dissolve solids and the organic layer was isolated. The aqueous layer was washed repeatedly with $CHCl_3$ and EtOAc, the organic layers were combined and dried with Na_2SO_4, then concentrated. The residue was chromatographed on silica eluting with a gradient of 0-30% EtOAc/Hexanes to give the product as a clear, colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.42 (q, *J*=7.15 Hz, 2H), 4.18 (t, *J*=6.4 Hz, 2H), 1.8 (p, *J*=6.4 Hz, 2H), 1.47 (p, *J*=7.4 Hz, 2H), 1.41 (t, *J*=7.15 Hz, 3H), 0.97 (t, *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 214.

Step 4: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

In a heavy walled round bottom flask with screw top were combined ethyl 5-butoxy-1,3-oxazole-2-carboxylate (2.53g, 11.88mmol) and 1-(4-fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one (1.22g, 5.94 mmol; see Example 1, Step 3) and trifluoroacetic acid (0.46ml, 5.94 mmol). The vessel was sealed and placed in an oil bath heated to 130 °C. The reaction mixture was stirred for 3 days. The dark brown reaction mixture was cooled and a crystalline precipitate formed. The mixture was diluted with ether and the solids collected by filtration and washed with ether to give the product as tan shiny plates. Further product can be obtained by evaporating the mother liquor, adding more trifluoroacetic acid and re-heating the mixture.

^1H NMR (400 MHz, $CDCl_3$) δ 12.9 (s, 1H), 8.42 (s, 1H), 7.31 (dd, *J*=5.3, 8.8 Hz, 2H), 7.06 (t, *J*=8.6 Hz, 2H), 4.72 (s, 2H), 4.41 (q, *J*=7.15 Hz, 2H), 3.50 (m, 4H), 1.41 (t, *J*=7.15 Hz, 3H) ppm. ES MS M+1 = 345.

Step 5: Ethyl 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

To a solution of chloroform (10 mL) and methanol (10 mL) was added trimethylsilyl diazomethane (2.0 M in hexanes, 5 ml, 0.01 mole). After stirring for 10 minutes at room temperature, 1-(ethoxycarbonyl)-6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-2-ium trifluoracetic acid salt (1.6 g, 3.5 mmol) in chloroform was added. After 7 hours, methanol (5 mL) and trimethylsilyl diazomethane (2.5 mL, 0.005 mole) was added to the reaction mixture. After 1 hour, glacial acetic acid (3 mL) was added with gas evolution observed. The solution was stirred for 0.5 hour. The product mixture was concentrated under vacuum. The residual material was subjected to column chromatography on silica gel eluting with 0-100 % ethyl acetate in hexanes. The appropriate fractions were combined and concentrated to afford the title compound as a foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.32 (dd, *J*=5.3, 8.5 Hz, 2H), 7.03 (t, *J*=8.6 Hz, 2H), 4.73 (s, 2H), 4.45 (q, *J*=7.14 Hz, 2H), 4.11 (s, 3H), 3.43 (t, *J*=6 Hz, 2H), 3.29 (t, *J*=6 Hz, 2H), 1.42 (t, *J*=7.2 Hz, 3H) ppm. ES MS M+1 = 359

Step 6: 6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (1.21 g, 3.38 mmol) in methanol (5 mL) and water (5 mL) and THF (5 mL) was added lithium hydroxide (0.425 g, 10.13 mmol). After 5 minutes, 1N HCl (3 equiv.) was added to the product mixture, which was then dried under vacuum to provide the crude title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (br, 1H), 8.35 (s, 1H), 7.27 (m, 2H), 7.03 (m, 2H), 4.73 (s, 2H), 4.15 (s, 3H), 3.55 (m, 4H) ppm. ES MS M+1 = 331

Step 7: 6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl chloride

A solution of 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carboxylic acid (1.11 g, 3.36 mmol) in thionyl chloride (0.4 g, 3.36 mmol) was heated to 110 °C. After 0.5 hours, the product mixture was concentrated under vacuum. The residue was suspended in toluene, evaporated, then suspended in chloroform and evaporated to give the title compound. The product was assayed by quenching in methanol solution to produce the methyl ester. ES MS M+1 = 345 (methyl ester forms after quench in methanol)

Step 8: 5-Amino-2-(4-fluorobenzyl)-8-methoxy-3,4-dihydro-2,6-naphthyridin-1(2H)-one

To a solution of sodium azide (0.24 g, 3.69 mmol) in water (2.5 mL) was added 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl chloride (1.17 g, 3.36 mmol) in acetone (15 mL). After 20 minutes, the product mixture was concentrated under vacuum to provide 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl azide. The crude azide (1.19 g, 3.35 mmol) in DMF (20 mL) was heated to 110 °C. After 20 minutes, the product mixture was cooled for 10 minutes, then 1N NaOH (3.3 mL) was added. After 20 minutes, the mixture was concentrated under vacuum, re-dissolved in toluene and $CHCl_3$ and evaporated. The residue was partitioned between $CHCl_3$ and saturated sodium bicarbonate. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.32 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.71 (s, 2H), 4.17 (s, 2H), 3.94 (s, 3H), 3.47 (t, *J*=6 Hz, 2H), 2.58 (t, *J*=6 Hz, 2H) ppm. ES MS (m+1) = 302.

Step 9: *N*-[6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]methanesulfonamide

To a solution of 5-amino-2-(4-fluorobenzyl)-8-methoxy-3,4-dihydro-2,6-naphthyridin-1(2H)-one (0.889 g, 2.95 mmol) in pyridine (5 mL) was added dropwise methanesulfonyl chloride (0.575 g, 5.016 mmol). After stirring for an hour at room temperature, the product mixture was quenched with pH 7 buffer, then concentrated under vacuum. The residue was dissolved in $CHCl_3$ and pH 7 buffer, the pH of the aqueous layer was adjusted to pH 5 with 1N NaOH and the layers separated. Several more extractions with $CHCl_3$ were performed. The organic extracts were dried with Na_2SO_4, filtered, and concentrated under vacuum, then dissolved in toluene and $CHCl_3$ and evaporated to provide the title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.70 (s, 2H), 4.03 (s, 3H), 3.44 (t, *J*=6.5 Hz, 2H), 3.21 (s, 3H), 2.89 (t, *J*=6.4 Hz, 2H) ppm. ES MS (m+1) = 380.

Step 10: *N*-[6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

To a solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]methanesulfonamide (0.097 g, 0.256 mmol) in DMF (2 mL) was added Cs_2CO_3 (0.083 g, 0.256 mmol) and MeI (0.04 g, 0.28 mmol, dissolved in DMF). After stirring for 2 hours, additional MeI (0.02 g, 0.14 mmol) was added. The product mixture was concentrated. The residue was partitioned between $CHCl_3$ and pH 7 buffer. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.26 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.70 (s, 2H), 4.06 (s, 3H), 3.43 (t, *J*=7 Hz, 2H), 3.21 (s, 3H), 3.03 (m, 5H) ppm. ES MS (m+1) = 394.

Step 11: *N*-[6-(4-Fluorobenzyl)-4-methoxy-2-oxido-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

To a solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.35 g, 0.89 mmol) in CH_2Cl_2 (10 mL) was added mCPBA (1.08 g, 6.23 mmol) in portions. After stirring for 3.5 hours at reflux, the product mixture was cooled to room temperature, 1 mL of ethanol was added, and the solution was concentrated. The residue was partitioned between $CHCl_3$ and saturated Na_2SO_3. The organic layer was extracted repeatedly with saturated sodium bicarbonate. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the crude title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.30(m, 2H), 7.03 (t, *J*=7 Hz, 2H), 4.72 (d, *J*= 14.6 Hz, 1H), 4.65 (d, J = 14.6 Hz, 1H), 4.01 (s, 3H), 3.45 (m, 2H), 3.29 (s, 3H), 3.20 (s, 3H), 3.18 (m, 1H), 2.87 (m, 1H) ppm. ES MS (m+1) = 410.

Step 12: *N*-[6-(4-Fluorobenzyl)-3-hydroxy-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

A solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-2-oxido-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.36 g, 0.889 mmol) in acetic anhydride (10 mL) was heated to 110 °C for 3 hours, then evaporated to dryness to give the intermediate 6-(4-fluorobenzyl)-4-methoxy-1-[methyl(methylsulfonyl)amino]-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-3-yl acetate (ES MS (m+1) = 452). The crude material was dissolved in methanol (6 mL) and treated with sodium methoxide (30 % by weight in methanol, 0.5ml, 2.6 mmol). After 1 hour, the product mixture was neutralized with 6 N HCl, then concentrated. The residue was partitioned between $CHCl_3$ and 10% $KHSO_4$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.71 (bs, 2H), 4.06 (s, 3H), 3.41 (t, *J*=6 Hz, 2H), 3.28 (s, 3H), 3.11 (s, 3H), 2.8 (m, 2H) ppm. ES MS (m+1) = 410.

Step 13: N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

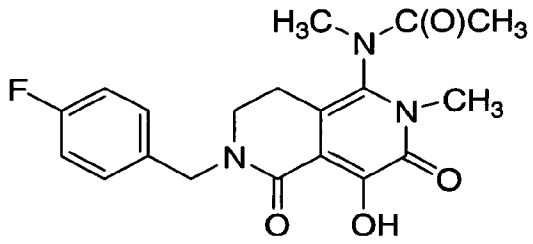
To a solution of *N*-[6-(4-fluorobenzyl)-3-hydroxy-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.0207 g, 0.506 mmol) in CH_2Cl_2 (6 mL) was added 30% by weight HBr in propionic acid (0.196 g HBr, 2.42 mmol). Alternatively, 30% HBr in acetic acid can be used. After 1.5 hours, the product mixture was evaporated and the residue partitioned between $CHCl_3$ and 10% $KHSO_4$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (br, 1H), 7.28 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.69 (s, 2H), 3.46 (t, *J*=7 Hz, 2H), 3.24 (s, 3H), 3.09 (s, 3H), 2.98 (m, 2H) ppm. ES MS (m+1) = 396.

EXAMPLE 9

N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-

methylacetamide



Step 1: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide

To 5-(ethoxycarbonyl)-2-(4-fluorobenzyl)-8-hydroxy-1-oxo-1,2,3,4-tetrahydro-2,6-naphthyridin-6-ium trifluoroacetate (0.5 gm, 1.09 mmol; see Example 8, Step 4) in glacial acetic acid (25 mL) at room temperature under nitrogen was added, with stirring, aqueous peroxide (30% by wt) (1.24 mL, 10.9 mmol). The reaction was warmed to 100 °C and stirred for 1.5 hours. The reaction was allowed to cool, ethanol (1 mL) was added and volatile components were removed under reduced pressure. The resulting oil was placed under high vacuum for 16 hours, then used as is. Alternatively, after cooling, water can be added and the volatile components removed under reduced pressure. The residue can be partitioned between $CHCl_3$ and saturated Na_2SO_3. The organic extract can be dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 12.8 (br, 1H), 7.90 (s, 1H), 7.28 (dd, J = 5.3, 8.5 Hz, 2H), 7.04 (t, J = 8.6 Hz, 2H), 4.69 (s, 2H), 4.43 (q, J = 7.14 Hz, 2H), 3.50 (t, J = 6.8 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 1.37 (t, J = 7.14 Hz, 3H) ppm. ES MS (m+1) = 361.

Step 2: Sodium 1-(ethoxycarbonyl)-6-(4-fluorobenzyl)-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-4-olate

To ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (2.3 gm, 6.38 mmol) in neat acetic anhydride (24 mL) was stirred under nitrogen at 100 °C for 1 hour. The reaction was concentrated to an oil under reduced pressure and dry methanol (20 mL) was added followed by a methanolic sodium methoxide solution (30% by wt) (4.54 mL, 25.2 mmol). The reaction was stirred at room temperature for 1 hour. The reaction was then concentrated to an oil under reduced pressure and crystallized from a small amount of methanol (~5 mL). The crystals were collected by filtration, washed an additional 10 mL of methanol and dried in vacuo to give the desired product.

^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (br, 1H), 7.30 (m, 2H), 7.06 (t, J=9 Hz, 2H), 4.71 (s, 2H), 4.36 (q, J=7 Hz, 2H), 3.44 (t, J=6 Hz, 2H), 3.33 (t, J=6 Hz, 2H), 1.38 (t, J=7 Hz, 3H) ppm. ES MS M+1 = 361.

Step 3: Ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of sodium 1-(ethoxycarbonyl)-6-(4-fluorobenzyl)-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-4-olate (1.45 g, 3.79 mmol) in DMF (20 mL) was added cesium carbonate (4.94 g, 15.1 mmol). After 5 minutes, methyl iodide (2.15 g, 15.1 mmol) was added. The reaction mixture was stirred at room temperature. After 24 hours, the product mixture was concentrated under vacuum. The residual material was subjected to column chromatography on silica gel eluting with 0-3 % methanol in CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the *N*- and *O*-methylated compounds separately.

N-methylated compound: Ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.02 (t, *J*=9 Hz, 2H), 4.69 (s, 2H), 4.39 (q, *J*=7 Hz, 2H), 4.13 (s, 3H), 3.51 (s, 3H), 3.53 (t, *J*=6 Hz, 2H), 2.59 (t, *J*=6 Hz, 2H), 1.38 (t, *J*=7 Hz, 3H) ppm. ES MS M+1 = 389.

O-methylated compound: Ethyl 6-(4-fluorobenzyl)-3,4-dimethoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.73 (s, 2H), 4.37 (q, *J*=7 Hz, 2H), 4.05 (m, 6H), 3.38 (t, *J*=6 Hz, 2H), 3.14 (t, *J*=6 Hz, 2H), 1.39 (t, *J*=7 Hz, 3H) ppm. ES MS M+1 = 389.

Step 4: 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (1.15 g, 2.96 mmol) in 1:1:1 MeOH/H_2O/THF (15 ml) was added LiOH (0.37g, 8.88 mmol) and the solution was stirred for 2 hours. A solution of 1 N HCl (8.9ml) was added, the solution was concentrated and $CHCl_3$ and 10% $KHSO_4$ were added. The layers were separated and the aqueous was extracted repeatedly. The combined organic layers were filtered and the solid collected. The remaining organic was dried over Na_2SO_4, filtered, combined with the collected solid and evaporated to give the crude product.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (dd, *J*=5.6, 8.6 Hz, 2H), 7.16 (t, *J*=8.8 Hz, 2H), 4.64 (s, 2H), 3.84 (s, 3H), 3.42 (s, 3H), 3.4 (t, *J*=6 Hz, 2H), 2.6 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 361.

Step 5: 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carbonyl chloride

To 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (0.213g, 0.6 mmol) was added thionyl chloride (5 mL) and the mixture was heated to reflux for 2 hours, then evaporated to dryness, suspended in toluene and evaporated three times to give the crude product.

^{1}H NMR (400 MHz, $CDCl^3$) δ 7.30 (dd, *J*=5.3, 8.6 Hz, 2H), 7.03 (t, *J*=8.8 Hz, 2H), 4.7 (s, 2H), 4.18 (s, 3H), 3.58 (s, 3H), 3.39 (t, *J*=6 Hz, 2H), 2.65 (t, *J*=6 Hz, 2H)ppm.

ES MS M+1 = 379.

Step 6: 5-amino-2-(4-fluorobenzyl)-8-methoxy-6-methyl-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione

To a solution of sodium azide (0.091g, 1.4 mmol) in 2 ml water cooled to 0 °C was add 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carbonyl chloride (0.48g, 1.28 mmol) in acetone (8 mL). The solution was stirred for 30 minutes, then evaporated. The residue was partitioned between $CHCl_3$ and saturated Na bicarbonate, dried with Na_2SO_4, filtered and evaporated to give the crude product, which was chromatographed on silica eluting with 5% MeOH/$CHCl_3$ saturated with NH_3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J*=5.5, 8.4 Hz, 2H), 7.01 (t, *J*=8.6 Hz, 2H), 4.7 (s, 2H), 4.05 (bs, 2H), 3.96 (s, 3H), 3.56 (s, 3H), 3.37 (t, *J*=6 Hz, 2H), 2.42 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 332.

Step 7: N-acetyl-N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide

To 5-amino-2-(4-fluorobenzyl)-8-methoxy-6-methyl-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione (0.119mg, 0.36 mmol) in a sealable microwave tube was added acetic anhydride (3.5 ml) and the solution was heated to 150 °C for 25 minutes in a microwave. The solution was evaporated to dryness to give the crude product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.02 (t, *J*=8.6 Hz, 2H), 4.69 (s, 2H), 4.14 (s, 3H), 3.37 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 2.37 (t, *J*=6 Hz, 2H), 2.32 (s, 6H)ppm.

ES MS M+1 = 416.

Step 8: N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide

To N-acetyl-N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide (0.149g, 0.36 mmol) in MeOH (5 mL) cooled to 0 °C was added 30% weight solution NaOMe in MeOH (0.2 ml, 1.07 mmol). The reaction was warmed to room temperature for 40 minutes, then 1 N HCl was added (1.07 mL) and the reaction was concentrated, and $CHCl_3$ and 10% $KHSO_4$ were added. The layers were separated and the aqueous was extracted repeatedly. The organic layer was dried over Na_2SO_4, filtered, combined with the collected solid and evaporated to give the crude product.

^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 7.26 (m, 2H), 7.01 (t, *J*=8.6 Hz, 2H), 4.65 (bs, 2H), 3.96 (s, 3H), 3.39 (s, 3H), 3.33 (t, *J*=6 Hz, 2H), 2.45 (bs, 2H), 2.23 (s, 3H)ppm. ES MS M+1 = 374.

Step 9: N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide

To N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide (0.073g, 0.196 mmol) in 2 mL DMF was added Cs_2CO_3 (0.084g, 0.25 mmol) and methyl iodide (0.044 mL, 0.7 mmole) and the reaction was stirred overnight at room temperature. The solvent was removed and the residue was partitioned between $CHCl_3$ and 10% $KHSO_4$, the organic was dried with Na_2SO_4, filtered and evaporated to give the crude product.

^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.4, 8.5 Hz, 2H), 7.03 (t, , *J*=8.6 Hz, 2H), 4.70 (s, 2H), 4.14 (s, 3H), 3.43 (s, 3H), 3.37 (m, 2H), 3.08 (s, 3H), 2.48 (m, 2H), 1.87 (s, 3H) ppm. ES MS M+1 = 388.

Step 10: N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide

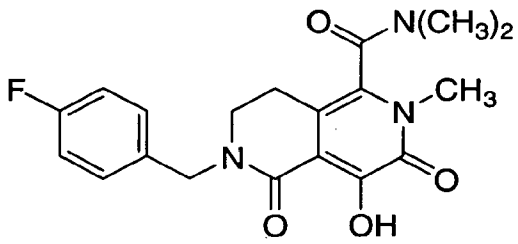
To N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide (0.070g, 0.181 mmol) was dissolved in 1 ml glacial acetic acid and 0.75 ml 30% by weight HBr in acetic acid solution was added. The reaction was stirred for 1.5 hours, water was added and the reaction evaporated to dryness under vacuum. The residue was purified on reverse phase and the fractions collected and evaporated. The residue was dissolved in dioxane, from which crystals formed and were collected. The crystals were dried under vacuum with heat to give the product.

^1H NMR (400 MHz, $CDCl_3$) δ 13.17 (s, 1H), 7.30 (dd, *J*=5.3, 8.7 Hz, 2H), 7.03 (t, , *J*=8.7 Hz, 2H), 4.73 (d, *J*=14.6 Hz, 1H), 4.66 (d, *J*=14.6 Hz, 1H), 3.44 (s, 3H), 3.41 (m, 2H), 3.08 (s, 3H), 2.61 (m, 2H), 1.86 (s, 3H) ppm.

ES MS M+1 = 374.

EXAMPLE 10

6-(4-Fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: Methyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.28 g, 0.81 mmol) in DMF (3.0 mL) was added Cs_2CO_3 (0.81 g, 2.47 mmol) at room temperature. After 10 minutes, CH_3I (0.597 g, 4.21 mmol) was added and the warmed to 40 °C. After 2.5 hours, the product mixture was partitioned between EtOAc and 1 N HCl. The organic extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated under vacuum. The residual material was subjected to column chromatography on silica gel eluting with 0-3 % methanol in CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the title compound. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2h), 7.02 (t, *J*=9 Hz, 2H), 4.68 (s, 2H), 4.12 (s, 3H), 3.91 (s, 3H), 3.48 (s, 3H), 3.32 (t, *J*=6 Hz, 2H), 2.56 (t, *J*=6.5 Hz, 2H) ppm. ES MS M+1 = 375.

Step 2: 6-(4-Fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

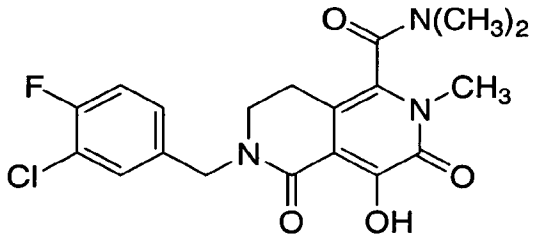
To a solution of methyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.575 g, 1.536 mmol) in methanol was added LiOH (0.11 g, 4.61 mmol) in water. The reaction mixture was heated to reflux. After 0.5 hours, the product mixture cooled to room temperature and concentrated under vacuum. The residual material was partitioned between EtOAc and 1 N HCl. The organic extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2h), 7.03 (t, *J*=9 Hz, 2H), 4.66 (s, 2H), 3.95 (s, 3H), 3.49 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 2.68 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 361.

Step 3: 6-(4-Fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

To a solution of 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (0.14 g, 0.40 mol) in DMF was added BOP (0.515 g, 1.167 mmol) and the dimethylamine (2.0 M in THF) (0.035 g, 0.778 mmol). After 24 hours, the product mixture was concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5-95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to give 6-(4-fluorobenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (ES MS M+1= 388) . A solution of this product (0.1 g, 0.3 mmol) in CH_2Cl_2 was treated with HBr (30 wt % in acetic acid) (0.104 g, 1.29 mmol) and after stirring at room temperature for 24 hours, concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound.
^{1}HNMR (400 MHz, CD_3OD) δ 7.38 (m, 2h), 7.04 (t, *J*=9 Hz, 2H), 4.66 (s, 2H), 3.49 (t, *J*=6 Hz, 2H), 3.43 (s, 3H), 3.08 (s, 3H), 2.93 (s, 3H), 2.59 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 374.

EXAMPLE 11

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

In a manner similar to that described for 6-(4-fluorobenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (Example 10, Step 3), 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide was prepared starting from p-methoxybenzyl chloride, and the material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA).
^{1}HNMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.82 (d, *J*=14.5 Hz, 1H), 4.46 (d, *J*=14.5 Hz, 1H), 4.07 (s, 3H), 3.78 (s, 3H), 3.45 (s, 3H), 3.40 (m, 1H), 3.30 (m, 1H), 3.09 (s, 3H), 2.90 (s, 3H), 2.51 (m, 1H), 2.35 (m, 1H) ppm. (ES MS M+1= 400.1)

Step 2: 4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

A solution of 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (0.18g, 0.45 mmol) in toluene (about 3 mL) was treated with p-toluene sulfonic acid (0.34g, 1.8 mmol). The mixture was heated to 110 °C for 4 hours, then cooled and concentrated under vacuum. The residue was partitioned between water and EtOAc, the aqueous layer concentrated,and the residue purified by reverse phase chromatography to give the title product.

^{1}HNMR (400 MHz, CD_3OD) δ 3.44 (m, 5H), 3.10 (s, 3H), 2.97 (s, 3H), 2.60 (t, *J*= 6.6 Hz, 2H) ppm. (ES MS M+1= 266.2)

Step 3: 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

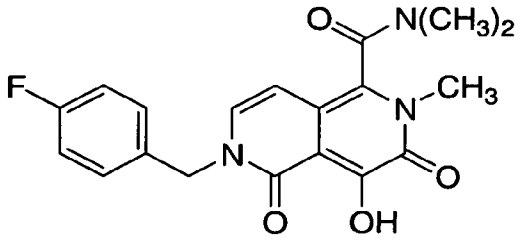
A solution of 4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (0.018g, 0.068 mmol) in DMF (2 mL) was treated with Cs_2CO_3 (0.066g, 0.2 mmol) and 3-chloro-4-fluoro benzyl bromide (0.045g, 0.2 mmol) and heated to 40 °C. The reaction mixture was then cooled to 0 degrees C, a suspension of NaH (95% dispersion in oil, 0.2 mmol) was added and the reaction was warmed to room temperature. After 1 hr the reaction was partitioned between ice water and EtOAc, the organic layer was dried with brine and Na_2SO_4, filtered and evaporated to give 6-(3-chloro-4-fluorobenzyl)-4-[(3-chloro-4-fluorobenzyl)oxy]-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (ES MS M+1= 549.9) . This material was then dissolved in CH_2Cl_2 (3 mL) and treated with 4 drops of a 30% by weight solution of HBr in propionic acid at room temperature. After 20 minutes the solution was concentrated and purified by reverse phase chromatography to give the product.

^{1}HNMR (400 MHz, CD_3OD) δ 7.48 (m, 1H), 7.32 (m, 1H), 7.22 (t, *J*=8.5 Hz, 1H), 4.76 (d, *J*=14.8 Hz, 1H), 4.63 (d, *J*=14.8 Hz, 1H), 3.50 (t, *J*=6.4 Hz, 2H), 3.44 (s, 3H), 3.08 (s, 3H), 2.95 (s, 3H), 2.61 (t, *J*=6.2 Hz, 2H) ppm. (ES MS M+1= 407.9)

EXAMPLE 12

6-(4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-

carboxamide



Step 1: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide

To solution of 5-(ethoxycarbonyl)-2-(4-fluorobenzyl)-8-hydroxy-1-oxo-1,2,3,4-tetrahydro-2,6-naphthyridin-6-ium trifluoroacetate (0.020g, 0.045 mmol; see Example 8, Step 4) in CCl_4 (2 mL) is added N-bromo succinimide (0.017g, 0.095 mmol) and AIBN(catalytic). The reaction is heated to 80 °C for 1 hour, then concentrated and chromatographed on reverse phase to give the product.

Step 2: 6-(4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide

The title compound can be prepared using a sequence of transformations similar to those described for Examples 9 and 10.

EXAMPLE 13

Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 50 mg of compound of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule. Encapsulated oral compositions containing any one of the compounds of Examples 2-12 can be similarly prepared.

EXAMPLE 14

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with WO 02/30930 for recombinant integrase. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds in Examples 1-11 were tested in the integrase assay and were found to have IC_{50}'s less than about 1 micromolar.

Further description on conducting the assay using preassembled complexes is found in Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

EXAMPLE 15

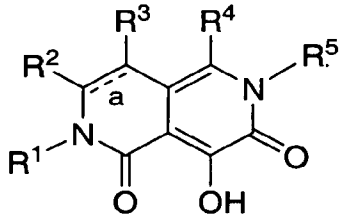
Assay for inhibition of HIV replication

Assays for the inhibition of acute HIV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. Representative compounds of the present invention exhibit inhibition of HIV replication in this assay. For example, the compounds in Examples 1-11 were found to have IC_{95}'s of less than about 10 micromolar in the present assay.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

R^1 is -C_{1-6} alkyl substituted with R^J, wherein R^J is:

(A) aryl or aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the aryl or fused aryl is:

(a) optionally substituted with from 1 to 5 substituents each of which is independently:

(1) -C_{1-6} alkyl optionally substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -NO_2, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO_2R^a, -S(O)$_n R^a$, -SO_2N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO_2R^b, -N(R^a)SO_2R^b, -N(R^a)SO_2N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,

(2) -O-C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -O-C_{1-6} haloalkyl,

(5) -OH,

(6) halogen,

(7) -CN,

(8) -NO_2,

(9) -N(R^a)R^b,

(10) -C(=O)N(R^a)R^b,

(11) -C(=O)R^a,

(12) -CO_2R^a,

(13) $-SR^a$,
(14) $-S(=O)R^a$,
(15) $-SO_2R^a$,
(16) $-SO_2N(R^a)R^b$,
(17) $-N(R^a)SO_2R^b$,
(18) $-N(R^a)SO_2N(R^a)R^b$,
(19) $-N(R^a)C(=O)R^b$,
(20) $-N(R^a)C(=O)-C(=O)N(R^a)R^b$, or
(21) $-N(R^a)CO_2R^b$, and

(b) optionally substituted with 1 or 2 substituents each of which is independently:
(1) phenyl,
(2) benzyl,
(3) -HetA,
(4) -C(=O)-HetA, or
(5) -HetB;

wherein each HetA is independently a C_{4-7} azacycloalkyl or a C_{3-6} diazacycloalkyl, either of which is optionally substituted with from 1 to 4 substituents each of which is independently oxo or C_{1-6} alkyl; and

wherein each HetB is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or hydroxy; or

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is
(i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or hydroxy; and
(ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or $-C_{1-6}$ alkyl substituted with aryl;

R^2 and R^3 are each independently -H or $-C_{1-6}$ alkyl;

R^4 is:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -C_{1-6} haloalkyl,

(4) -C_{1-6} alkyl substituted with -OH, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, -CN, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$C(=O)$-$N(R^a)$-C_{1-6} alkylene-OR^b with the proviso that the -$N(R^a)$- moiety and the -OR^b moiety are not both attached to the same carbon of the -C_{1-6} alkylene- moiety, -$S(O)_nR^a$, -$SO_2N(R^a)R^b$, -$N(R^a)C(=O)$-R^b, -$N(R^a)CO_2R^b$, -$N(R^a)SO_2R^b$, -$N(R^a)SO_2N(R^a)R^b$, -$N(R^a)C(=O)N(R^a)R^b$, or -$OC(=O)N(R^a)R^b$,

(5) -$C(=O)R^a$,

(6) -CO_2R^a,

(7) -$C(=O)N(R^a)R^b$,

(8) -$C(=O)$-$N(R^a)$-C_{1-6} alkylene-OR^b with the proviso that the -$N(R^a)$- moiety and the -OR^b moiety are not both attached to the same carbon of the -C_{1-6} alkylene- moiety,

(9) -$N(R^a)$-$C(=O)$-R^b,

(10) -$N(R^a)$-$C(=O)$-$C(=O)N(R^a)R^b$,

(11) -$N(R^a)SO_2R^b$,

(12) -$N(R^a)SO_2N(R^a)R^b$,

(13) -$N(R^a)SO_2N(R^a)R^b$,

(14) -$N(R^a)C(=O)N(R^a)R^b$,

(15) -$OC(=O)N(R^a)R^b$,

(16) -R^K,

(17) -$C(=O)$-R^K,

(18) -$C(=O)N(R^a)$-R^K,

(19) -$C(=O)N(R^a)$-C_{1-6} alkylene-R^K,

(20) -C_{1-6} alkyl substituted with -R^K,

(21) -C_{1-6} alkyl substituted with -$C(=O)$-R^K,

(22) -C_{1-6} alkyl substituted with -$C(=O)N(R^a)$-R^K, or

(23) -C_{1-6} alkyl substituted with -$C(=O)N(R^a)$-C_{1-6} alkylene-R^K;

wherein R^K is

(i) C_{3-8} cycloalkyl, which is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(ii) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-$N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)R^a$, -C_{1-6} alkylene-CO_2R^a, -C_{1-6} alkylene-$S(O)_nR^a$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halogen, -$N(R^a)R^b$, -$C(=O)N(R^a)R^b$, -$C(=O)R^a$, -CO_2R^a, -$S(O)_nR^a$, or -$SO_2N(R^a)R^b$;

(iii) HetK, which is a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:

(a) optionally substituted with from 1 to 6 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; and

(b) optionally substituted with aryl or HetC;

wherein HetC is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and the optionally fused heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy; or

(iv) HetL, which is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

R^5 is:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -C_{3-8} cycloalkyl optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(4) -C_{1-6} alkyl substituted with C_{3-8} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, or -O-C_{1-6} haloalkyl,

(5) -C_{1-6} alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 5 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} alkylene-OH, -C_{1-6} alkylene-O-C_{1-6} alkyl, -C_{1-6} alkylene-O-C_{1-6} haloalkyl, -C_{1-6} alkylene-$N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)N(R^a)R^b$, -C_{1-6} alkylene-$C(=O)R^a$, -C_{1-6} alkylene-CO_2R^a, -C_{1-6} alkylene-$S(O)_nR^a$, -O-C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} haloalkyl, -OH, halogen, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^a$, $-S(O)_nR^a$, or $-SO_2N(R^a)R^b$;

(6) -C_{1-6} alkyl substituted with HetD, wherein HetD is

(i) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is optionally substituted with from 1 to 5 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or oxo; or

(ii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

each aryl is independently phenyl, naphthyl, or indenyl;

each R^a is independently H or C_{1-6} alkyl;

each R^b is independently H or C_{1-6} alkyl; and

each n is independently an integer equal to zero, 1, or 2.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-CH_2-R^J$.

3. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein R^J is phenyl optionally substituted with from 1 to 3 substitutents each of which is independently:

(1) -C_{1-4} alkyl,
(2) -C_{1-4} haloalkyl,
(3) -O-C_{1-4} alkyl,
(4) halogen,
(5) -CN,
(6) -C(=O)N(R^a)R^b, or
(7) -SO_2R^a.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein R^J is 4-fluorophenyl.

5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{1-6} fluoroalkyl,
(4) -CO_2R^a,
(5) -C(=O)N(R^a)R^b,
(6) -C(=O)-N(R^a)-$(CH_2)_{2-3}$-OR^b,
(7) -N(R^a)-C(=O)-R^b,
(8) -N(R^a)SO_2R^b,
(9) -N(R^a)SO_2N(R^a)R^b,
(10) -R^K,
(11) -C(=O)-R^K, or
(12) -C(=O)N(R^a)-$(CH_2)_{0-2}$-R^K.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^5 is:

(1) -H,
(2) -C_{1-4} alkyl,

(3) -C_{3-6} cycloalkyl optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, or -O-C_{1-4} haloalkyl,

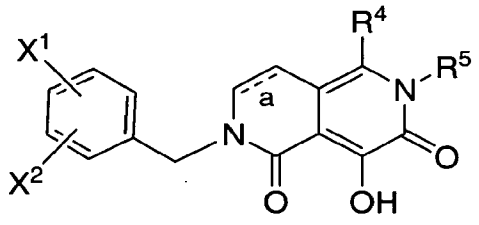
(4) -$(CH_2)_{1-2}$-C_{3-6} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, or -O-C_{1-4} haloalkyl,

(5) -$(CH_2)_{1-2}$-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-4} alkyl, -C_{1-4} alkylene-O-C_{1-4} alkyl, -C_{1-4} haloalkyl, or -O-C_{1-4} haloalkyl, or

(6) -$(CH_2)_{1-2}$-HetD, wherein HetD is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-4} alkyl, -C_{1-4} haloalkyl, -O-C_{1-4} alkyl, -O-C_{1-4} haloalkyl, or hydroxy;

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are both -H.

8. A compound of Formula II, or a pharmaceutically acceptable salt thereof:



(II)

wherein:

bond " $\overset{a}{=\!=\!=}$ " in the ring is a single bond or a double bond;

X^1 and X^2 are each independently:

(1) -H,

(2) -C_{1-6} alkyl,

(3) -O-C_{1-6} alkyl,

(4) -C_{1-6} haloalkyl,

(5) -O-C_{1-6} haloalkyl,

(6) halogen,

(7) -CN,

(8) -$N(R^a)R^b$,

(9) -$C(=O)N(R^a)R^b$,

(10) -$S(O)_nR^a$, wherein n is an integer equal to zero, 1, or 2,

(11) -$N(R^a)SO_2R^b$,

(12) -$N(R^a)SO_2N(R^a)R^b$,

(13) -$N(R^a)C(=O)R^b$,

(14) -$N(R^a)C(=O)$-$C(=O)N(R^a)R^b$,

(15) -HetA,

(16) -C(=O)-HetA, or

(17) HetB;

wherein each HetA is independently a C_{4-5} azacycloalkyl or a C_{3-4} diazacycloalkyl, either of which is optionally substituted with 1 or 2 substituents each of which is independently oxo or C_{1-6} alkyl; and with the proviso that when HetA is attached to the rest of the compound via the -C(=O)- moiety, the HetA is attached to the -C(=O)- via a ring N atom; and

each HetB is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -C_{1-6} haloalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} haloalkyl, or hydroxy;

R^4 is:

(1) -CO_2R^a,

(2) -$C(=O)N(R^a)R^b$,

(3) -$C(=O)$-$N(R^a)$-$(CH_2)_{2-3}$-OR^b,

(4) -$N(R^a)C(=O)R^b$,

(5) -$N(R^a)SO_2R^b$,

(6) -HetK,

(7) -C(=O)-HetK,

(8) -C(=O)N(R^a)-(CH_2)$_{0-1}$-(C_{3-6} cycloalkyl), wherein the cycloalkyl is optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C_{1-6} alkyl, -CF_3, -O-C_{1-6} alkyl, or -OCF_3, or

(9) -C(=O)N(R^a)-CH_2-phenyl, wherein the phenyl is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl, -O-C_{1-6} alkyl, -CF_3, -OCF_3, or halogen;

wherein HetK is a 5- or 6-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is optionally substituted with from 1 to 4 substituents each of which is independently -C_{1-6} alkyl or oxo; and with the proviso that when HetK is attached to the rest of the compound via the -C(=O)- moiety, the HetK is attached to the -C(=O)- via a ring N atom;

R^5 is:

(1) -H,
(2) -C_{1-6} alkyl,
(3) -C_{3-6} cycloalkyl,
(4) -CH_2-C_{3-6} cycloalkyl, or
(5) -CH_2-phenyl;

each R^a is independently H or C_{1-6} alkyl; and

each R^b is independently H or C_{1-6} alkyl.

9. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein:

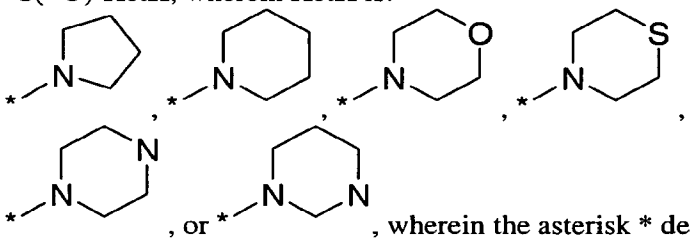
X^1 and X^2 are each independently:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{1-4} haloalkyl,
(4) -O-C_{1-4} alkyl,
(5) halogen,

(6) -CN,
(7) -C(=O)NH_2,
(8) -C(=O)NH(-C_{1-4} alkyl),
(9) -C(=O)N(-C_{1-4} alkyl)$_2$, or
(10) -SO_2-C_{1-4} alkyl;

R^4 is:

(1) -CO_2H,
(2) -C(=O)-O-C_{1-4} alkyl,
(3) -C(=O)NH_2,
(4) -C(=O)NH-C_{1-4} alkyl,
(5) -C(=O)N(C_{1-4} alkyl)$_2$,
(6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,
(7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,
(8) -NHC(=O)-C_{1-4} alkyl,
(9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl,
(10) -$NHSO_2$-C_{1-4} alkyl,
(11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl,
(12) -C(=O)-HetK, wherein HetK is:



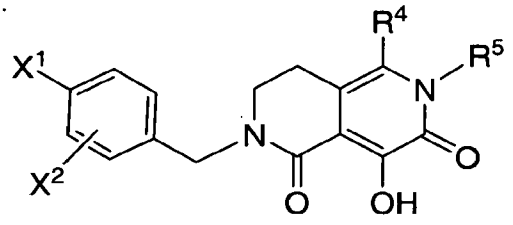
, wherein the asterisk * denotes the point of attachment to the rest of the compound,
(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),
(14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),
(15) -C(=O)NH-CH_2-phenyl, or
(16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

R^5 is:

(1) -H,
(2) -C_{1-4} alkyl,
(3) -C_{3-6} cycloalkyl,
(4) -CH_2-C_{3-6} cycloalkyl, or

(5) -CH_2-phenyl.

10. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, which is a compound of Formula III:



(III)

wherein:

X^1 is:

(1) -H,
(2) bromo,
(3) chloro,
(4) fluoro, or
(5) methoxy;

X^2 is:

(1) -H,
(2) bromo,
(3) chloro,
(4) fluoro,
(5) methoxy,
(6) -C_{1-4} alkyl,
(7) -CF_3,
(8) -O-C_{1-4} alkyl,
(9) -OCF_3,
(10) -CN, or
(11) -SO_2(C_{1-4} alkyl);

R^4 is:

(1) $-CO_2H$,

(2) $-C(=O)-O-C_{1-4}$ alkyl,

(3) $-C(=O)NH_2$,

(4) $-C(=O)NH-C_{1-4}$ alkyl,

(5) $-C(=O)N(C_{1-4}$ alkyl$)_2$,

(6) $-C(=O)-NH-(CH_2)_{2-3}-O-C_{1-4}$ alkyl,

(7) $-C(=O)-N(C_{1-4}$ alkyl$)-(CH_2)_{2-3}-O-C_{1-4}$ alkyl,

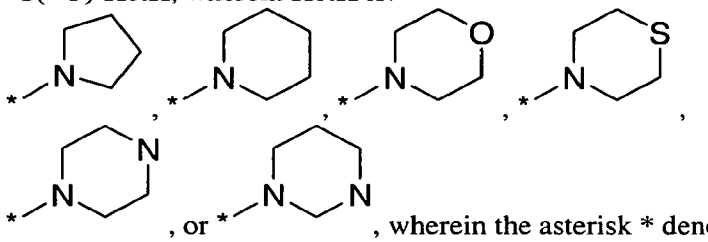
(8) $-NHC(=O)-C_{1-4}$ alkyl,

(9) $-N(C_{1-4}$ alkyl$)C(=O)-C_{1-4}$ alkyl,

(10) $-NHSO_2-C_{1-4}$ alkyl,

(11) $-N(C_{1-4}$ alkyl$)SO_2-C_{1-4}$ alkyl,

(12) -C(=O)-HetK, wherein HetK is:



, or

, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) $-C(=O)NH-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl),

(14) $-C(=O)N(C_{1-4}$ alkyl$)-(CH_2)_{0-1}-(C_{3-6}$ cycloalkyl),

(15) $-C(=O)NH-CH_2$-phenyl, or

(16) $-C(=O)N(C_{1-4}$ alkyl$)-CH_2$-phenyl; and

R^5 is:

(1) -H,

(2) $-C_{1-4}$ alkyl,

(3) cyclopropyl,

(4) cyclobutyl,

(5) $-CH_2$-cyclopropyl,

(6) $-CH_2$-cyclobutyl, or

(5) $-CH_2$-phenyl.

11. The compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein

X^1 is fluoro;

X^2 is -H;

R^4 is:

(1) -C(=O)-O-C_{1-3} alkyl,

(2) -C(=O)NH-C_{1-3} alkyl,

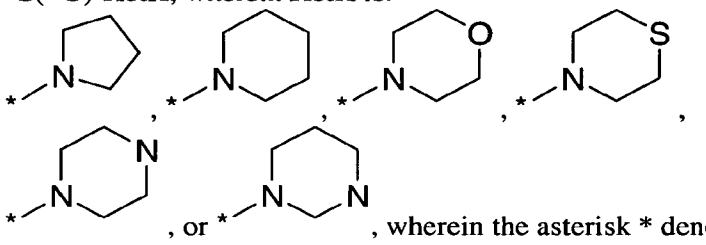
(3) -C(=O)N(C_{1-3} alkyl)$_2$,

(4) -C(=O)-N(C_{1-3} alkyl)-$(CH_2)_2$-O-C_{1-3} alkyl,

(5) -N(C_{1-3} alkyl)C(=O)-C_{1-3} alkyl,

(6) -N(C_{1-3} alkyl)SO_2-C_{1-3} alkyl,

(7) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(8) -C(=O)NH-$(CH_2)_{0-1}$-(cyclopropyl),

(9) -C(=O)NH-$(CH_2)_{0-1}$-(cyclobutyl),

(10) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclopropyl,

(11) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl,

(12) -C(=O)NH-CH_2-phenyl, or

(13) -C(=O)N(C_{1-3} alkyl)-CH_2-phenyl; and

R^5 is -H.

12. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate;

6-(4-fluorobenzyl)-4-hydroxy-*N*,*N*-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N-cyclobutyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N-cyclopropyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-*N*-isopropyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-N-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid;

N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide;

N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide;

6-(4-fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide; and

6-(4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide.

13. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

14. A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

15. A method for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

16. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for inhibiting HIV integrase in a subject in need thereof.

17. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.

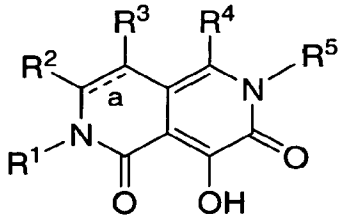
18. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for inhibiting HIV integrase in a subject in need thereof.

19. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.

20. A pharmaceutical combination which is (i) a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and (ii) an HIV infection/AIDS antiviral agent selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors; wherein the compound of (i) or its pharmaceutically acceptable salt and the HIV infection/AIDS antiviral agent of (ii) are each employed in an amount that renders the combination effective for inhibiting HIV integrase, for preventing or treating infection by HIV, or for preventing, treating or delaying the onset of AIDS.

ABSTRACT OF THE DISCLOSURE

Hydroxy (tetra- or hexa-)hydronaphthyridine dione compounds of Formula I are inhibitors of HIV integrase and inhibitors of HIV replication:



(I)

wherein a, R^1, R^2, R^3, R^4 and R^5 are defined herein. The compounds are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. The compounds are employed against HIV infection and AIDS as compounds per se or in the form of pharmaceutically acceptable salts. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines.